Objective: To investigate the preliminary safety and efficacy of apremilast, an oral phosphodiesterase 4 inhibitor, for atopic dermatitis.

Design: This investigator-initiated, open-label pilot study evaluated 2 doses of apremilast in patients with atopic dermatitis. Differential gene analysis was performed from peripheral whole blood using data before and after treatment.

Setting: University-based dermatology clinical research unit.

Patients: Sixteen adult patients with atopic dermatitis.

Intervention: A specific phosphodiesterase 4 inhibitor, apremilast.

Main Outcome Measures: The primary outcome was incidence of adverse events. Secondary outcomes included the differences in pruritus, Dermatology Life Quality Index (DLQI), and Eczema Area and Severity Index (EASI) scores between the baseline visit and end-of-study visit for each cohort.

Results: The group receiving apremilast, 20 mg twice daily, displayed a significant reduction from baseline of pruritus ($P = .02$) and the DLQI ($P = .003$) at 3 months. The group receiving apremilast, 30 mg twice daily, displayed a significant reduction of the EASI ($P = .008$) and the DLQI ($P = .01$) at 3 months. At 6 months, there was a significant reduction of the EASI ($P = .002$), the visual analog scale ($P = .03$), and the DLQI ($P = .03$). Gene ontologic analyses comparing baseline with samples during treatment revealed alterations in immune response pathways, especially those related to cyclic adenosine monophosphate–mediated signaling.

Conclusions: These results support further development of apremilast for treatment of atopic dermatitis. Larger randomized controlled studies are needed to more adequately evaluate both safety and efficacy. Limitations include the small sample size and absence of a control.

Trial Registration: clinicaltrials.gov Identifier: NCT01393158


M O D E R A T E T O S E V E R E
atopic dermatitis (AD) often cannot be adequately controlled with topical agents. Consequently, many patients with AD are treated with systemic corticosteroids, cyclosporine, azathioprine, and methotrexate that carry the risks associated with immunosuppression or can lead to end-organ damage.⁴ A safe, effective systemic therapy for patients with AD is greatly needed. It has been known since the 1980s that leukocytes from patients with AD display elevated phosphodiesterase (PDE) activity compared with normal controls, which leads to leukocyte hyperactivity and inflammation.² ³ There are 11 different human PDE isoenzymes in the human body known to date. PDE type 4 (PDE4) is one of the major PDEs expressed in leukocytes.³ ⁵ Inhibitors of PDE4 cause accumulation of intracellular cyclic adenosine monophosphate (cAMP), which in turn activates protein kinase A (PKA) and other downstream effectors, resulting in inhibition of proinflammatory cytokine transcription and other cellular responses, such as neutrophil degranulation, chemotaxis, and adhesion to endothelial cells.⁶

Inhibitors of PDE have been developed, and they provide clinical benefit in patients with AD when used topically,⁷ ⁸ although no compounds have been brought to the marketplace. Oral inhibitors of PDE4 have been studied for treatment of asthma,
chronic obstructive pulmonary disease, psoriasis, and psoriatic arthritis, but not for AD.10 Apremilast is a novel oral agent that modulates multiple anti-inflammatory pathways through targeted PDE4 inhibition. Apremilast has pharmacodynamic properties with potential therapeutic benefit for treating inflammatory disorders that involve elevated serum cytokine levels. In human cellular models, apremilast inhibited production of inflammatory mediators such as tumor necrosis factor (TNF), interleukin 12 (IL-12), IL-2, interferon γ (IFN-γ), IL-5, IL-8, leukotriene B4 (LTB4), and the adhesion molecule CD18/CD11b (Mac-1) (Figure 1). In addition, apremilast is known to augment IL-10 production, which is a known suppressor of other proinflammatory chemokines.11,12 To assess the safety and efficacy, and possible mechanism of action of apremilast in AD, we conducted an open-label prospective trial of apremilast in 16 adult patients with moderate to severe AD.

### METHODS

**CLINICAL METHODS**

This study was approved by the Oregon Health and Science University (Portland) institutional review board, and informed consent was obtained from all patients. This was an investigator-initiated, open-label pilot study examining 2 doses of apremilast, N-[2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl) ethyl]-1,3-dioxoisindolin-4-yl]acetamide (S-enantiomer) for adult AD. A total of 16 patients with moderate to severe AD were treated with apremilast in 2 different cohorts. Cohort 1 consisted of 6 adult patients treated with apremilast, 20 mg twice a day, for a total of 3 months. At the conclusion of this cohort, the US Food and Drug Administration (FDA) approved a higher dose and longer treatment course for apremilast. Thus, a second cohort was initiated. Cohort 2 consisted of 10 adult patients treated with apremilast, 30 mg twice a day, for a total of 6 months. A diagnosis of AD was determined by the Hanifin-Rajka criteria.13 The primary outcome for the study was incidence of adverse events (AEs), with secondary outcomes focusing on disease severity measures and peripheral whole-blood gene expression changes.

Efficacy of apremilast was assessed at each study visit using the Eczema Area and Severity Index (EASI),14 Dermatology Life Quality Index (DLQI), investigator global assessment (IGA), and the visual analog scale (VAS) for pruritus. Patients were monitored for AEs and improvement in eczema as determined by the EASI, DLQI, and VAS for pruritus at 1 week, 2 weeks, 4 weeks, and every 4 weeks thereafter in cohort 1 and at 2 weeks, 4 weeks, and every 4 weeks thereafter in cohort 2. After the last dose of medication, patients in both cohorts were asked to return for a 4-week follow-up visit. To participate in the study, patients must have met the following inclusion criteria: age of at least 18 years at time of consent, disease severity of at least 6 on the Rajka-Langeland15 severity scoring system, EASI score of at least 11, and be a candidate for or previously receiving systemic therapy. In addition, patients were required to remain on a stable regimen of triamcinolone acetonide ointment, 0.1%, for 2 weeks prior to the start of the study and throughout the trial. Most patients applied the ointment twice a day 2 times a week. No other topical therapy except emollients was allowed.

Patients were excluded if they had a history of active mycobacterial infection with any species (including *Mycobacterium tuberculosis*) within 3 years prior to the screening visit, or if they had a diagnosis of psoriasis, psoriatic arthritis, or ankylosing spondylitis.

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**Figure 1.** The role of phosphodiesterase type 4 (PDE4) in inflammation. An overview of the proposed mechanism of action in various cell types derived from in vivo studies. CCL indicates C-C motif ligand; CXCL, C-X-C motif ligand; GM-CSF, granulocyte macrophage colony-stimulating factor; HLA-DR, human leukocyte antigen-DR; ICAM-1, intercellular adhesion molecule-1; IFN, interferon; IL, interleukin; iNOS, inducible nitric oxide synthase; LTB4, leukotriene B4; Mac-1, adhesion molecule CD18/CD11b; NK, natural killer; and TNF, tumor necrosis factor. (Figure reproduced with permission from Celgene Corp.)
latent or incompletely treated M tuberculosis infection, as indicated by a positive purified protein derivative skin test. Patients were not allowed to participate in the trial if they had had at least 3 major bacterial infections resulting in hospitalization and/or requiring intravenous antibiotic treatment within the past 2 years; clinically significant abnormality on chest radiography at screening; use of any investigational medication or systemic medication within 4 weeks prior to the start of the study drug or 3 pharmacokinetic/pharmacodynamic half-lives (whichever was longer); any clinically significant abnormality on 12-lead electrocardiogram at screening; a history of congenital or acquired immunodeficiency; positive results at screening for antinuclear antibody, hepatitis B surface antigen or hepatitis C; a history of genital or acquired immunodeficiency; positive results at screening for human immunodeficiency virus infection; malignant disease or a history of malignant disease (except for treated [ie, cured] basal cell skin carcinomas > 3 years prior to screening); systemic corticosteroid–dependent asthma; or active infection of any type at the time of enrollment.

STATISTICAL ANALYSIS

A sample size of 10 patients was initially determined to provide adequate preliminary data regarding the safety of apremilast in this patient population. The patient number was increased to 16 when a new cohort (cohort 2) was started to examine a higher dose of apremilast that was approved by the FDA for study. Intent-to-treat analyses were performed using the last observation carried forward method for patients who discontinued the study or who required potent topical steroid rescue. For per-protocol analyses, only patients with available data were included. This analysis included the scores in patients who required potent topical steroid rescue. We used t tests for analyses of continuous variables.

MICROARRAY ANALYSES

As an exploratory end point to potentially identify immune pathways affected by apremilast, peripheral whole blood was obtained for differential gene expression analyses at baseline and after 3 (cohort 1) and 6 (cohort 2) months of treatment to determine apremilast’s potential mechanism of action in patients with AD. RNA isolation and microarray analyses were performed in the Oregon Health and Science University Gene Microarray Shared Resource. Total RNA was isolated from PAXGene tubes using the PAXGene Blood RNA Isolation kit (QIAGEN Inc.). RNA quantity was measured by spectrophotometric analysis; RNA quality was evaluated by size analysis on the Bioanalyzer 2100 (Agilent Technologies Inc.). All samples passed RNA quality assessment review.

RNA samples were labeled using the Ovation WTA Pico Amplification and Labeling System (NuGEN Technologies Inc.). Fifty nanograms of each sample were amplified with the Ovation WTA Pico kit, converted to sense complementary DNA (cDNA) with the WT-Ovation Exon Module, version 1, kit, and labeled with the Encore Biotin Module kit. Hybridization and array processing were performed as described in the NuGEN Encore Biotin Module User Guide (http://www.nugeninc.com/tasks/sites/nugen/assets/File/user_guides/userguide_encore_biotin.pdf). Two micrograms of each labeled cDNA target were hybridized with the GeneChip Human Gene 1.0 ST array (Affymetrix) and scanned on the Affymetrix GeneChip 3000 Scanner. The array image was processed with Affymetrix Command Console (version 3.1.1). Data were normalized using the robust multichip average method.

Differential expression analyses were performed on 16 paired samples. All putatively differentially expressed genes were based on false discovery rate–adjusted P values < .05. Based on the putative differentially expressed gene list, both enriched pathways and functional gene ontologic characteristics were identified (P < .05 for hypergeometric test) in the GoStats package within the Bioconductor statistical programming environment (http://www.bioconductor.org).

RESULTS

Sixteen patients with moderate to severe AD were included in this open-label study. Patients were divided into 2 cohorts. The 6 patients in cohort 1 received apremilast, 20 mg twice daily for 3 months, and the 10 patients in cohort 2 received apremilast, 30 mg twice daily, for a total of 6 months. Population demographics are shown in Table 1. Almost all patients had received systemic therapy in the past. In cohort 1, 3 patients had an IGA of severe disease, and 1 patient had an IGA of very severe disease. In cohort 2, 8 of 10 had moderate disease, and 2 of 10 had severe disease as measured by the IGA.

ADVERSE EVENTS

Nausea was the most common AE and seemed to be dose related (33% in cohort 1, 90% in cohort 2). In all pa-
tients the nausea was rated as mild and improved over
the course of the study. Other AEs were rated as mild,
with the exception of herpes zoster, and improved over
the course of the study (eTable, http://www.archdermatol
.com). Only 1 patient (patient 5) was withdrawn from
the study owing to an AE, the onset of herpes zoster af-
after 2 weeks of taking apremilast, 20 mg twice daily
(eTable). Two patients in cohort 2 (patients 11 and 12)
required rescue with clobetasol propionate, 0.05%, oint-
ment once daily for 1 week, owing to a disease flare. Pa-
tient 11 required the rescue medication after 2 months,
and patient 12 required rescue medication after 4 months.

EFFICACY AT 3 MONTHS IN COHORTS 1 AND 2

In both cohorts 1 and 2, a trend toward improvement was
seen in all outcomes (Figure 2). Intent-to-treat analy-
ses performed at 3 months revealed significant reduc-
tion of itch from baseline (VAS) and improvement in qual-
ity of life (DLQI) in cohort 1 (P = .02 and P = .003,
respectively). Disease severity (EASI) and quality of life
(DLQI) improved in cohort 2 (P = .008 and P = .01, re-
spectively). Statistically significant clinical improve-
ment in AD was noted within the first 2 weeks of study
drug in cohort 2 (P = .03). Patients experienced an
average reduction in itch of 49% using a VAS, from a mean
baseline of 62.3 mm to 30.5 mm in cohort 1 and a 25% reduc-
tion in cohort 2, from 45.8 mm to 32.4 mm (Figure 3). The EASI scores reduced an average of 19% in
cohort 1 from a mean baseline of 30.9 to 22.1 and an
average of 39% in cohort 2, from a mean baseline of 21.4
to 13.2 (Figure 2) at 3 months. The DLQI scores reduced
an average of 55% in cohort 1, from a mean baseline of
14.2 to 6.2 (Figure 4) and an average of 58% in cohort 2,
from a mean baseline of 10.1 to 3.8. In cohort 1, patients
reported a statistically significant decline in pruritus within
the first 2 weeks of use (P = .045) with a trend for a decline
in pruritus in cohort 2 (P = .06) (Figure 3). In cohort 1, 1
of 6 patients reduced their IGA score by 1 U (eg, from very
severe to severe) (Figure 5). Two of 10 patients in co-
hort 2 reduced their IGA score by 1 U (Figure 6). No
patient in either cohort reached an IGA score of clear or
almost clear at the 3-month time point. One patient achieved
an IGA score of mild in cohort 2.

EFFICACY AT 6 MONTHS IN COHORT 2

Evaluation of cohort 1 was concluded at 3 months; conse-
quently, no 6-month data were available for that cohort.
Statistically significant improvement was seen in all outcomes

\[ \text{Figure 3. Mean visual analog scale (VAS) scores for pruritus at different time}
\text{points with error bars representing standard deviations.} \]

\[ \text{Figure 4. Mean Dermatology Life Quality Index (DLQI) scores per cohort at}
\text{different time points with error bars representing the standard deviations.} \]

\[ \text{Figure 5. Distribution of investigator global assessment (IGA) scores in cohort}
\text{1 (pretreatment and posttreatment with apremilast, 20 mg twice a day).} \]

\[ \text{Figure 6. Distribution of investigator global assessment scores at 3 months in}
\text{cohort 2 (pretreatment and posttreatment with apremilast, 30 mg twice a day).} \]
at 6 months in cohort 2 (Figures 3, 4, and 10). Intent-to-treat analyses revealed significant reduction in EASI, from 21.1 to 11.6 (P = .002); VAS, from 45.8 mm to 25.3 mm (P = .03); and the DLQI, from 10.1 mm to 4.2 mm (P = .03). Per protocol, EASI reduced from 21.1 to 10.4 (P = .001), VAS from 45.8 to 22.7 (P = .01), and DLQI from 10.1 to 4.0 (P = .02). The number of patients who improved or worsened with the different outcomes is shown in Figures 7, 8, and 9. Five patients (50%) improved at least 1 U in the IGA at 6 months. Four of these 5 reached an IGA of mild, and 1 achieved an IGA of almost clear (Figure 11). More detailed information regarding cohort 2 responses for each outcome is shown in Figures 7, 8, and 9.

POST HOC EFFICACY ANALYSES ON COHORTS COMBINED

Post hoc intent-to-treat analyses performed on combined data from both cohorts were performed to improve the power of our analyses. The data from both cohorts combined showed statistically significant improvement in all outcomes. The EASI score was reduced from a mean baseline of 24.8 to 16.2 (P = .002), the VAS was reduced from a mean baseline of 52.0 mm to 31.7 mm (P = .003), and the DLQI was reduced from a mean baseline of 11.6 to 4.7 (P = .001). Post hoc per-protocol analyses, which included data from all patients who were able to finish the study, also revealed significance in all outcomes (EASI, P = .001; VAS, P = .007; DLQI, P = .001).

PERIPHERAL BLOOD GENE EXPRESSION ANALYSIS

In cohort 1, gene expression data revealed significant differential expression of the cAMP response element binding (CREB) pathway (P = 3.19 × 10^-4) and BAD (bcl-2 antagonist of cell death) phosphorylation pathway (P = 2.34 × 10^-5). In addition, gene ontology analyses of biological processes revealed significant differential expression of chemokine-mediated signaling (P = 9.5 × 10^-4), IL-12 signaling (P < .05), cytokine remodeling (P < .05), and regulation of immune complex clearing by monocytes and macrophages.
Apremilast seemed to be a safe and tolerable systemic therapy in our small cohort of adult patients with AD, with nausea being the most common AE. The clinical responses seen at 6 months with apremilast (>50% improvement in EASI) are similar to responses seen with immunosuppressant medications currently used in treating AD.1 While this pilot study was uncontrolled and open label, the efficacy data suggest that apremilast provided clinically meaningful improvement in several disease parameters. Combined, these data support the development of a future controlled study for moderate to severe AD in adults. Given the lack of any FDA-approved systemic medications for AD, the further development of candidate drugs for this condition is greatly needed.

Current therapy for moderate severe disease in AD includes phototherapy, methotrexate, azathioprine, cyclosporine, and mycophenolate. Phototherapy, while safe and effective, is limited by its inconvenience for the patient. Cyclosporine is the best studied and most effective systemic therapy for AD but is limited by nephrotoxicity. Mycophenolate may be a safer option than cyclosporine, but in a recent comparison trial with cyclosporine, patients receiving mycophenolate sodium required several oral steroid rescues. Methotrexate and azathioprine are both limited by their relatively modest efficacy (<50% reduction in EASI at 12 weeks in 1 recent comparative study) and their potential for hepatic and hematologic toxic reaction. In the current study, the reduction in EASI scores seen at the 6-month time point would suggest the efficacy of apremilast to be on par with the responses seen with traditional agents. An advantage of apremilast over these other agents is the lack of end-organ toxicity. The data thus far with apremilast suggest no significant renal, hepatic, or hematologic toxic reaction concerns. Randomized, placebo-controlled studies are needed to determine more accurate estimates of efficacy and safety in this population.

(P=1.9 × 10^-6) (Table 2). In cohort 2, there was significant differential expression of CCR3 signaling in eosinophils (P=5.497 × 10^-2).

The mechanism by which apremilast may work in AD is not known, although it has many anti-inflammatory effects. By blocking PDE4 activity, apremilast affects several cell types in the immune system, including monocytes, dendritic cells, neutrophils, T cells, natural killer cells, and macrophages. Because immune cells in AD are known to have elevated PDE activity,24 we hypothesized that apremilast would reverse this abnormality unique to AD and return immune cells to a less active state. Specifically, apremilast may improve AD by way of inhibiting the expression of T-cell cytokines previously reported to be increased in AD such as IFN-γ, TNF, IL-5, IL-13, and IL-17.

Unfortunately, whole-blood RNA profiling in this study failed to identify gene pathways that were replicated in both study cohorts, although significant changes in gene expression were found in some pathways that may be relevant to AD. The CREB pathway had significant differential expression in cohort 1. CREB is a transcription factor with multiple downstream effects on gene expression in various cell types. CREB has been shown to be both anti-inflammatory and proinflammatory in immune and epithelial cells. CREB is activated by phosphorylation by various kinases, 1 of which being PKA. PKA is directly influenced by increased levels of intracellular cAMP, as would be seen with a PDE4 inhibitor. The role of the CREB pathway in AD is unknown at this time. The BAD phosphorylation pathway also had significant differential expression in cohort 1. The unphosphorylated form of BAD is well known to be a proapoptotic factor by binding to bcl-2, consequently inhibiting its anti-apoptotic action. One of PKA’s many targets is BAD, which effectively inactivates the pathway. Interestingly, increased levels of bcl-2 have been shown in patients with AD treated with UV light, inferring that bcl-2 may have a role in AD. Finally, IL-12 and CCR3 signaling pathways were also found to be significant. CCR3 is a chemokine receptor for eotaxin—a chemokine found to be elevated in the lesional skin of patients with AD. Likewise, elevated expression of IL-12 has been reported in the lesional skin and blood of patients with AD. Modifications of these immune pathways by apremilast may account for some of the beneficial effect in AD, but more detailed analyses of these pathways are necessary.

Given the drug’s broad anti-inflammatory profile, apremilast is being evaluated for activity in various inflammatory skin diseases, such as psoriasis (clinicaltrials.gov: NCT01194219), psoriatic arthritis (clinicaltrials.gov: NCT01194219), and rheumatoid arthritis (clinicaltrials.gov: NCT00565342).
NCT01172938), and cutaneous lupus (clinicaltrials.gov: NCT00708916). Most recently, a 352-patient, multicenter controlled study was carried out in which patients with psoriasis achieved a significant dose-dependent improvement in disease severity with apremilast therapy, and pivotal phase 3 studies are under way for this disease.

Limitations of the current study include its small sample size and the possibility of bias or confounding. First, patients with severe disease may naturally get better (regression to the mean). Second, patients may adhere to topical treatment regimens better during clinical studies. We attempted to reduce the chance of an effect of the concomitant topical steroid use by ensuring that patients were receiving stable doses of topical steroids 2 weeks prior to study drug initiation. Topical steroid use then continued at a stable dose or could be discontinued.

In summary, our preliminary data indicate that apremilast significantly improves inflammation, pruritus, and quality of life in patients with AD with mild and generally well-tolerated AEs. Larger randomized controlled studies are needed to further assess its safety and efficacy in AD.

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Additional Contributions: Kristina Vartanian, PhD, and Shannon McWeeny, PhD, performed the gene arrays and analyzed the gene expression data. Christine E. Carocci provided editing assistance and Jon M. Hanifin, MD, pioneered the work regarding the role of PDE in AD that inspired the development of this study.
Abraham Buschke in Ghetto Terezin: A Remembrance

In 1945, an obituary in this journal began:

We have learned with deep sorrow that Abraham Buschke, a dermatologist of unusual gifts and brilliant ideas, died two years ago in Theresienstadt [Czechoslovakia]. His wife, his faithful companion of many years, was released from that vast concentration camp and permitted to enter Switzerland a few weeks ago. She brought news of his death.1

Abraham Buschke (1868-1943), who for many years served as Chief of Dermatology at the Rudolf Virchow Hospital in Berlin, was one of Germany's leading dermatologists. He was dismissed from this position in 1933, following the Nazi takeover, because he was Jewish. Dr Buschke's many contributions to dermatology, which are discussed in several literary tributes, included the first description of scleredema and his description with Helen Ollendorff of dermatofibrosis lenticularis disseminata (the Buschke-Ollendorff syndrome).1,2,3 This article focuses on Dr Buschke's fate as a prisoner in Terezin (Theresienstadt).

Dr Buschke and his wife, Erna, were rounded up by the Nazis from their Berlin home on November 4, 1942, and taken by train (transport I-75) to Terezin, which is located in what is now the Czech Republic (death certificate of Dr Abraham Buschke, provided by the Jewish Museum, Prague, Czech Republic). Terezin was a ghetto that was established by the Nazis to concentrate the Jews of Czechoslovakia, Germany, and other countries until they could be transferred to death camps.

When the Buschkes arrived at Terezin, the ghetto was already severely overcrowded, food was in short supply, and epidemics claimed thousands of lives. The Buschkes were housed in block E VII (the Kavalier Barracks) but in different communal rooms, since men and women were separated. Erna Buschke, in a biography, describes her husband's struggles in Terezin:

Although suffering from severe sickness, he wished fervently, even in Theresienstadt, to accomplish a lot and to use his vast experience to help his fellow inmates. He was particularly concerned about the skin diseases due to avitaminosis and vermin (especially lice) that he hoped to conquer by the use of thallium.1

Dr Buschke unfortunately died of severe enteritis on February 25, 1943. According to the Terezin Memorial, Czech Republic, his body was cremated, and his ashes were placed in a box and stored in a section of the ghetto called the Columbarium. In November 1944, his ashes and those of 20,000 inmates were thrown into the River Ohre (Eger), as the Nazis tried to conceal their crimes.

The Nobel laureate, author, and Holocaust survivor Elie Wiesel was asked if he knew "the response to Auschwitz." He answered "that not only do I not know it, but that I don't even know if a tragedy of this magnitude has a response. What I do know is that there is 'response' in responsibility."4 As caring human beings, we are all responsible for one another. That responsibility includes doing everything we can to end hatred and inhumanity. Let the fulfillment of this lofty goal be our tribute to Dr Abraham Buschke, a great dermatologist, who perished in Ghetto Terezin almost 70 years ago.

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