

OPA-15406, a novel, topical, nonsteroidal, selective phosphodiesterase-4 (PDE4) inhibitor, in the treatment of adult and adolescent patients with mild to moderate atopic dermatitis (AD): A phase-II randomized, double-blind, placebo-controlled study

Jon M. Hanifin, MD,^a Charles N. Ellis, MD,^b Ilona J. Frieden, MD,^c Regina Fölster-Holst, MD,^d
Linda F. Stein Gold, MD,^e Angelo Secci, MD,^f Angela J. Smith, PA,^f Cathy Zhao, PhD,^f
Elena Kornyeveva, MD, PhD,^f and Lawrence F. Eichenfield, MD^g

Portland, Oregon; Ann Arbor and Detroit, Michigan; San Francisco and San Diego, California;
Kiel, Germany; and Princeton, New Jersey

Background: Peripheral leukocytes in patients with atopic dermatitis (AD) have elevated phosphodiesterase-4 activity, which is associated with production of proinflammatory mediators. OPA-15406 is a phosphodiesterase-4 inhibitor with high selectivity for phosphodiesterase-4-B.

Objectives: We sought to assess effectiveness and tolerability of topical OPA-15406 in patients with AD.

Methods: This was a randomized, double-blind, vehicle-controlled, phase-II study. Patients 10 to 70 years of age with mild or moderate AD received topical OPA-15406 0.3% (n = 41), OPA-15406 1% (n = 43), or vehicle (n = 37) twice daily for 8 weeks.

Results: The primary end point, Investigator Global Assessment of Disease Severity score of 0 or 1 with greater than or equal to 2-grade reduction, was met at week 4 in the OPA-15406 1% group ($P = .0165$ vs vehicle). Mean percentage improvement from baseline Eczema Area and Severity Index score for OPA-15406 1% was notable in week 1 (31.4% vs 6.0% for vehicle; $P = .0005$), even larger in week 2 (39.0% vs 3.0%; $P = .0001$), and persisted for 8 weeks. Visual analog scale pruritus scores improved from moderate to mild within the first week in the OPA-15406 1% group (36.4% mean change; $P = .0011$). OPA-15406 levels in blood were negligible. Incidence of adverse events was low, with most events mild in intensity.

From Oregon Health and Science University^a; Department of Dermatology, University of Michigan Medical School, Ann Arbor^b; University of California, San Francisco School of Medicine^c; University Clinics of Schleswig-Holstein, Campus Kiel, Germany^d; Henry Ford Health Systems, Detroit^e; Otsuka Pharmaceutical Development and Commercialization Inc, Princeton^f; and University of California, San Diego School of Medicine and Rady Children's Hospital.^g

Supported by Otsuka Pharmaceutical Development and Commercialization Inc, Rockville, MD.

Disclosure: Dr Hanifin served as a consultant to Anacor Pharmaceutical, Dermira, Leo Pharma, and Otsuka Pharmaceuticals and participated in studies in recent years for Pfizer, Merck, Chugai Pharmaceutical, and Anacor Pharmaceuticals. Dr Ellis served as a consultant to Celgene Corporation, Ferndale Healthcare, Johnson & Johnson, and Otsuka Pharmaceutical. Dr Frieden serves as the chair of the data and safety monitoring board for this OPA-15406 phase-II study, is an advisor for Galderma SA and Anacor Pharmaceuticals, and is a consultant with Laboratoires Pierre Fabre. Dr Fölster-Holst participated in studies in recent years for Novartis International AG, Astellas Pharma, Laboratoires Pierre Fabre, Regeneron Pharmaceuticals, and Pharmanet AG; delivered presentations for La Roche-Posay,

ALK, Abbott Laboratories, and Neubourg GmbH; served on an advisory board for Johnson & Johnson; and is a member of the data and safety monitoring board for this OPA-15406 phase-II study. Dr Stein Gold is a member of the data and safety monitoring board for this OPA-15406 phase-II study and is an advisor and investigator for Anacor Pharmaceuticals and an investigator for GSK. Drs Secci, Zhao, and Kornyeveva and Ms Smith are employees of Otsuka Pharmaceutical Development and Commercialization Inc. Dr Eichenfield served as a consultant and investigator for Anacor Pharmaceuticals and Otsuka Pharmaceutical.

Accepted for publication April 3, 2016.

Reprint requests: Elena Kornyeveva, MD, PhD, Otsuka Pharmaceutical Development and Commercialization Inc, 508 Carnegie Center, Princeton, NJ 08540. E-mail: elena.kornyeveva@otsuka-us.com.

Published online May 14, 2016.

0190-9622

© 2016 by the American Academy of Dermatology, Inc. Published by Elsevier, Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

<http://dx.doi.org/10.1016/j.jaad.2016.04.001>

Limitations: Further confirmatory phase-III studies are required.

Conclusion: OPA-15406 ointment may provide an effective therapeutic modality for patients with mild to moderate AD. (J Am Acad Dermatol <http://dx.doi.org/10.1016/j.jaad.2016.04.001>.)

Key words: atopic dermatitis; atopic eczema; OPA-15406; phosphodiesterase type 4 inhibitor; topical agents; topical calcineurin inhibitor.

This study was conducted in compliance with International Conference on Harmonization good clinical practice guidelines for conducting, recording, and reporting clinical trials, and for archiving essential documents.¹ Consistent with ethical principles for the protection of human research subjects,² no trial procedures were performed on trial candidates until written consent had been obtained. The informed consent form, protocol, and amendments for the study were submitted to and approved by the institutional review board or independent ethics committee for each respective trial site or country.

Atopic dermatitis (AD) is a chronic inflammatory skin condition characterized by pruritic erythematous skin lesions and associated cutaneous dysfunction (eg, barrier-disrupted skin).³ The onset of AD occurs most commonly between 3 and 6 months of age, with approximately 60% of patients developing the condition in the first year of life and 90% by 5 years of age.⁴⁻⁶ The majority of affected individuals have resolution of disease during childhood, although 10% to 30% of patients maintain the condition throughout their lives, and a small number of others develop first symptoms as adults.^{4,7} It has been estimated that approximately 18 million people are living with AD in the United States, many with undiagnosed disease.⁸

AD cannot be cured, but prompt and effective management can greatly improve both the symptoms and quality of life of affected individuals. According to guidelines from the American Academy of Dermatology,⁴ when emollient use and good skin care are insufficient to control AD, pharmacologic treatment should start with mild- to moderate-potency topical corticosteroids. If this approach is unsuccessful, treatment with calcineurin inhibitors can be considered. For severe AD that remains refractory to topical agents, treatment may be

CAPSULE SUMMARY

- Peripheral leukocytes of patients with atopic dermatitis have increased phosphodiesterase activity.
- OPA-15406, a new topical inhibitor of phosphodiesterase-4, provided rapid and sustained relief of patient-reported pruritus and significant overall improvement of atopic dermatitis.
- OPA-15406-mediated selective phosphodiesterase-4 inhibition may provide an effective treatment modality for patients with atopic dermatitis.

intensified to ultraviolet phototherapy and systemic immunomodulators. Although current pharmacotherapeutic approaches have proven to be efficacious in clinical trials,^{4,9-13} each has limitations. Extended use of topical corticosteroids is associated with cutaneous atrophy³ and can sometimes have systemic side effects, such as suppression of the hypothalamic-pituitary-adrenal axis, especially in children.¹⁴ Available topical calcineurin inhibitors carry boxed warnings posing

some limitations on their long-term use, based on possible associations with lymphomas and skin malignancies in animal studies.^{15,16} However, clinical studies in human beings have failed to identify an association between topical calcineurin inhibitor use and malignancies,¹⁷ with the possible exception of a very slightly increased risk of skin lymphomas in patients with severe AD.¹⁸

Peripheral blood leukocytes in patients with AD have increased phosphodiesterase-4 (PDE4) activity,¹⁹⁻²¹ which has been associated with higher production of the proinflammatory mediators tumor necrosis factor- α , interleukin (IL)-17, IL-22, and interferon- γ and lower production of the anti-inflammatory mediator IL-10.²¹ In pharmacologic analyses, the new chemical entity OPA-15406 exhibited highly selective inhibitory activity against PDE4 subtypes, particularly subtype B (IC₅₀ = 11.2 nmol/L), and improved skin condition in relevant animal models of AD (unpublished data). This report evaluates the clinical activity, pharmacokinetics, and tolerability of 2 concentrations of OPA-15406 ointment in adult and adolescent patients with mild or moderate AD.

METHODS

Study design

This was a phase-II, randomized, double-blind, vehicle-controlled, parallel-group study. Eligible

Abbreviations used:

AD:	atopic dermatitis
BSA:	body surface area
DLQI:	Dermatology Life Quality Index
EASI:	Eczema Area and Severity Index
IGA:	Investigator Global Assessment of Disease Severity
IL:	interleukin
PDE4:	phosphodiesterase-4
VAS:	visual analog scale

patients were between the ages of 10 and 70 years and had a diagnosis of AD according to the criteria of Hanifin and Rajka²² and Rajka and Langeland,²³ a baseline Investigator Global Assessment of Disease Severity (IGA) score of 2 (mild) or 3 (moderate), and at least a 3-year history of the disease. Total body surface area (BSA)²⁴ affected by AD at baseline could not be more than 40%, but had to be at least 5%. The face, neck, and head were not treated under the protocol. Patients were required to have had a previous positive but inadequate response to 1 or more standard therapies for AD or were currently unable to use a previously successful treatment. Exclusion criteria included having received systemic therapy or phototherapy within 28 days, or use of topical corticosteroids or calcineurin inhibitors within 7 days of study entry.

Eligible patients were randomized into 3 treatment groups to receive OPA-15406 0.3% (wt/wt), OPA-15406 1% (wt/wt), or vehicle on a double-blind basis. During the 8-week treatment period, patients were instructed to apply a thin film of study ointment to affected areas twice daily, with applications occurring approximately 12 hours apart. The amount applied was approximately 1 g of ointment per every 4% BSA to be treated. Assessments were conducted pretherapy (baseline) and at weeks 1, 2, 4, 6, and 8.

Thirty dermatology-specialty research centers participated in the study from the United States ([ClinicalTrials.gov](https://clinicaltrials.gov) identifier: NCT02068352), Poland (European Clinical Trials Database number: 2013-003899-12), and Australia.

Assessments

Patients were assessed at each visit by a board-certified dermatologist or country-specific equivalent using the 6-point IGA (0 = no disease to 5 = very severe disease)⁴ and the Eczema Area and Severity Index (EASI).²⁵ Patient-reported effects were based on a 100-mm visual analog scale (VAS) for pruritus,²⁶ the adult Dermatology Life Quality Index (DLQI)²⁷ for patients 17 years of age or older,

and the Children's DLQI²⁸ for patients 16 years of age or younger.

Pharmacokinetics

Nine patients from 6 centers also consented to provide blood samples at baseline and week 4 for pharmacokinetic evaluation of OPA-15406 (5 in the 0.3% group and 4 in the 1% group). Blood samples were collected before and 2, 4, and 8 hours after the first of the twice-daily doses. Plasma samples were analyzed by high-performance liquid chromatography with tandem mass spectrometric detection. Pharmacokinetic parameters were determined using noncompartmental analysis performed with Phoenix WinNonlin, Version 6.3 (Pharsight Corporation, Princeton, NJ).

Statistical analysis

Forty patients per treatment group provided more than 80% power for each comparison of OPA-15406 versus vehicle at a 2-sided significance level 0.05, assuming response rates of 0.53 and 0.20, respectively. The primary end point was incidence of success at week 4 in IGA score, defined as a final score of 0 or 1 with at least a 2-grade reduction from baseline. To control the overall type I error rate of 0.05, a 2-step testing procedure was applied: OPA-15406 1% versus vehicle first, and OPA-15406 0.3% versus vehicle next only if the first test was statistically significant ($P < .05$).

For the primary analysis, patients without an IGA score at a scheduled visit were treated as nonresponders for that visit. Comparisons of incidences of success between each OPA-15406 level and vehicle were conducted by Cochran-Mantel-Haenszel test, stratified by geographic region and age group. The 95% Wald confidence intervals were calculated for the differences of incidence between each OPA-15406 concentration level and vehicle. Subgroup analyses for the primary efficacy variable were provided by age group (<18 or ≥18 years), geographic region, IGA (mild, moderate), and percent BSA treated (5%-25%, >25%) at baseline.

Change (or percentage change) from baseline in overall IGA score, EASI score, VAS score, and DLQI were analyzed using analysis of covariance with treatment, region, and age group as fixed terms and baseline score as covariate, based on last observation carried forward data.

RESULTS

Patients

A total of 121 patients were randomly assigned to receive OPA-15406 0.3% (n = 41), OPA-15406 1% (n = 43), or vehicle (n = 37) (Fig 1). All patients

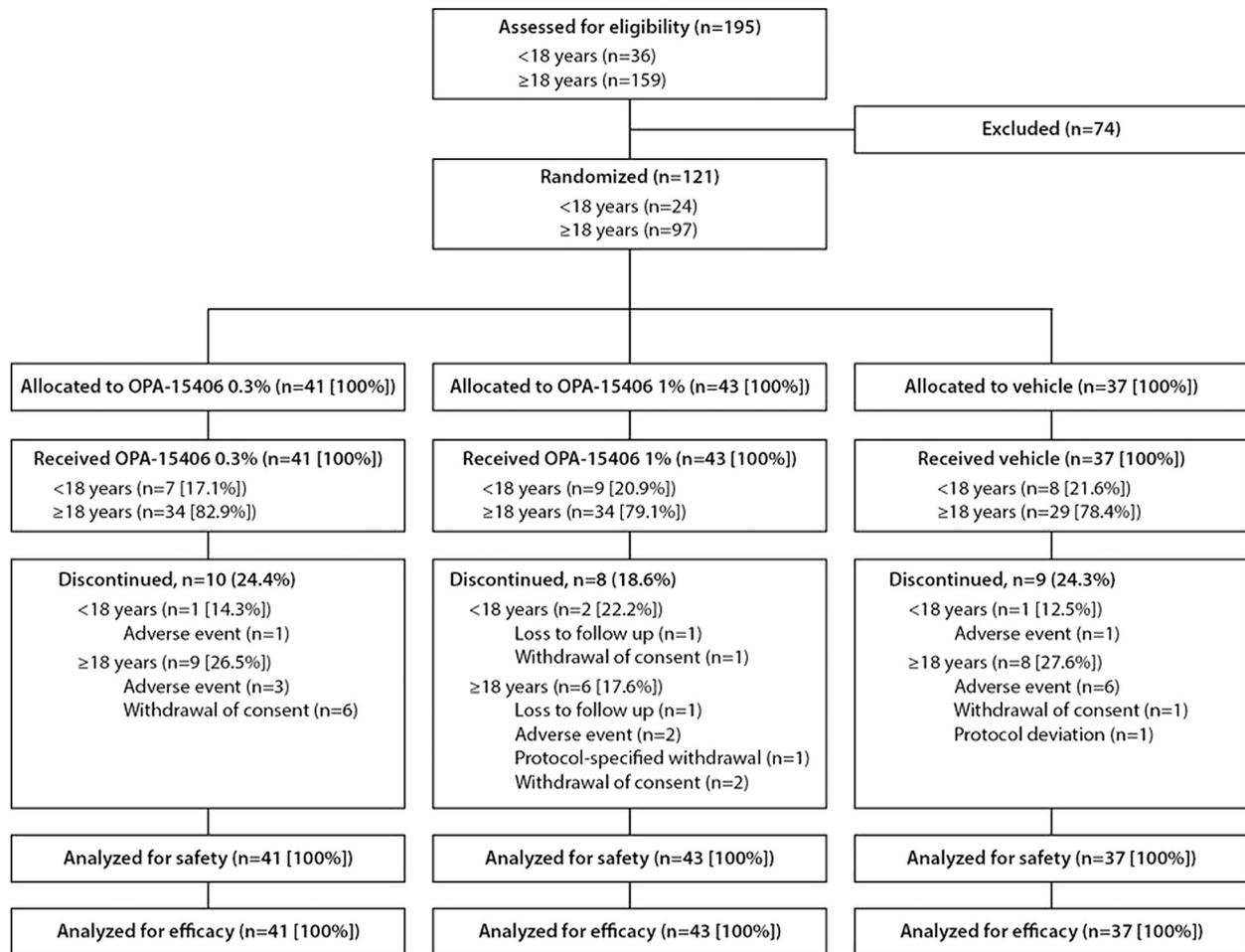


Fig 1. CONSORT flow diagram.

received at least 1 dose of study ointment and were analyzed for efficacy and safety. Overall, 27 (22%) patients discontinued prematurely, 10 (24%) in the OPA-15406 0.3% group, 8 (19%) in the OPA-15406 1% group, and 9 (24%) in the vehicle group. Three of the early discontinuations were attributed to adverse events potentially related to study treatment, including 1 case of worsening erythema/pruritus (OPA-15406 0.3%), 1 case of AD exacerbation (vehicle), and 1 case of application site irritation (vehicle). One protocol-specified withdrawal occurred because of pregnancy in a patient who received 30 days of OPA-15406 1%; the patient subsequently delivered a full-term healthy baby.

In all, 37 (31%) patients enrolled with an IGA score of 2 and 84 (69%) patients enrolled with an IGA score of 3. At baseline, the overall study population had a mean EASI score of 9.5 ± 5.2 , a mean VAS pruritus score of 61.7 ± 24.0 mm, and a mean affected BSA percentage of $13\% \pm 8.6\%$. Of enrolled patients, 20% were younger than 18 years of age. Baseline characteristics were adequately balanced among treatment groups (Table 1).

Effectiveness

The prespecified primary end point was the rate of successful responses on the IGA at week 4. A successful response was defined as a score of 0 (clear) or 1 (almost clear), with at least a 2-grade reduction from the baseline score of 2 (mild) or 3 (moderate). At week 4, success rates were 2.7% for vehicle, 14.6% for OPA-15406 0.3% ($P = .0690$ vs vehicle), and 20.9% for OPA-15406 1% ($P = .0165$ vs vehicle) (Fig 2, A). No appreciable subgroup differences were observed in success rate when analyzed by age, percentage of affected BSA at baseline, or geographic region (Fig 3), although patients with a baseline IGA score of 3 demonstrated a numerically better IGA response rate than those with a baseline IGA score of 2.

Mean rates at which patients reached an IGA score of 0 or 1, with or without a 2-grade reduction from baseline score, were 10.0% for vehicle, 24.4% for OPA-15406 0.3% ($P = .1287$ vs vehicle), and 30.2% for OPA-15406 1% ($P = .0354$ vs vehicle) at week 4 (Fig 2, B). Whether based on IGA success rate (Fig 2, A) or an IGA score of 0 or 1 (Fig 2, B), disease

Table I. Demographic and baseline characteristics

	OPA-15406 0.3%			OPA-15406 1%			Vehicle		
	Age <18 y	Age ≥18 y	Total	Age <18 y	Age ≥18 y	Total	Age <18 y	Age ≥18 y	Total
N	7	34	41	9	34	43	8	29	37
Age, y, mean ± SD	14.6 ± 2.3	40.9 ± 12.5	36.4 ± 15.2	14.0 ± 2.4	39.4 ± 14.4	34.1 ± 16.5	12.6 ± 2.6	37.6 ± 13.1	32.2 ± 15.6
Male gender, n (%)	3 (42.9)	11 (32.4)	14 (34.1)	4 (44.4)	17 (50.0)	21 (48.8)	4 (50.0)	10 (34.5)	14 (37.8)
Race, n (%)									
White	3 (42.9)	21 (61.8)	24 (58.5)	6 (66.7)	24 (70.6)	30 (69.8)	4 (50.0)	24 (82.8)	28 (75.7)
Black/African American	2 (28.6)	12 (35.3)	14 (34.1)	3 (33.3)	8 (23.5)	11 (25.6)	2 (25.0)	3 (10.3)	5 (13.5)
Asian	0 (0.0)	1 (2.9)	1 (2.4)	0 (0.0)	1 (2.9)	1 (2.3)	0 (0.0)	2 (6.9)	2 (5.4)
Other*	2 (28.6)	0 (0.0)	2 (4.9)	0 (0.0)	1 (2.9)	1 (2.3)	2 (25.0)	0 (0.0)	2 (5.4)
Body surface treated, n (%)									
≥5% to <10%	2 (28.6)	14 (41.2)	16 (39.0)	6 (66.7)	14 (41.2)	20 (46.5)	2 (25.0)	11 (37.9)	13 (35.1)
≥10% to <20%	2 (28.6)	10 (5.5)	12 (29.3)	2 (22.2)	11 (32.4)	13 (30.2)	2 (25.0)	13 (44.8)	15 (40.5)
≥20% to <30%	2 (28.6)	5 (14.7)	7 (17.1)	0 (0.0)	7 (20.6)	7 (16.3)	3 (37.5)	2 (6.9)	5 (13.5)
≥30% to ≤40%	1 (14.3)	5 (14.7)	6 (14.6)	1 (11.1)	2 (5.9)	3 (7.0)	1 (12.5)	3 (10.3)	4 (10.8)

*American Indian, Alaska Native, Native Hawaiian, other Pacific Islander, or other.

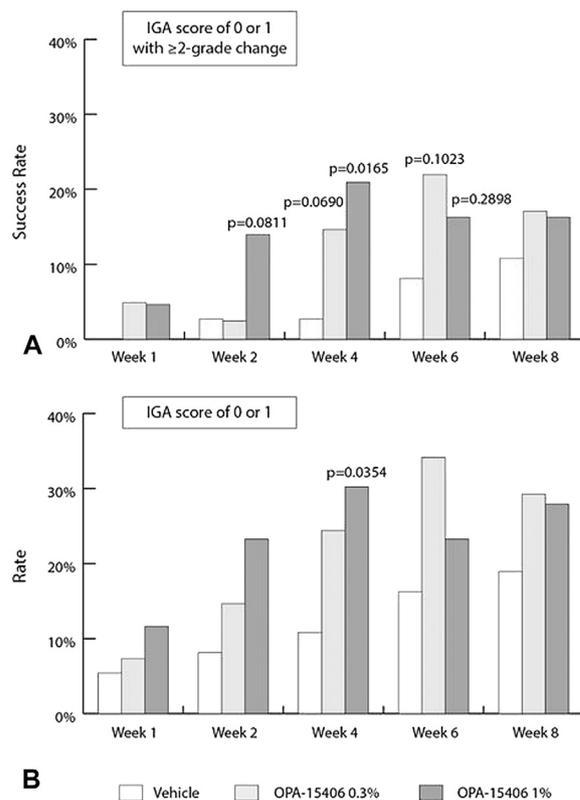


Fig 2. Clinician-reported outcomes based on Investigator Global Assessment of Disease Severity (IGA). **A**, Mean success rates per visit. A successful response was defined as an IGA score of 0 or 1 with at least a 2-grade reduction from baseline. **B**, Mean rates of an IGA score of 0 or 1 (ie, with or without a 2-grade reduction) per visit. *P* values are for comparisons with vehicle. Last observation carried forward was used to impute missing data.

severity improved relatively rapidly (week 2-4) in the OPA-15406 1% group, and early positive responses were sustained until the end of treatment (week 8) (Fig 2).

EASI mean scores decreased (indicating disease improvement) at week 1 in the OPA-15406 1% treatment group (-2.37 ; $P = .0098$ vs vehicle), and this trend was maintained at all subsequent study time points (Fig 4, A). This translated into a 31.4% improvement at week 1 ($P = .0005$ vs vehicle [6.0%]), a 39.0% change by week 2 ($P = .0001$ vs vehicle [3.0%]), and a sustained response through week 8 (Fig 4, B). EASI percentage changes from baseline were also numerically improved at all time points in the OPA-15406 0.3% group ($P = .0303$ OPA-15406 0.3% vs vehicle at week 2), although the treatment effects were smaller than those observed with OPA-15406 1%.

In patient-reported assessments, the OPA-15406 1% group exhibited a rapid and sustained improvement in AD-associated pruritus relative to the vehicle

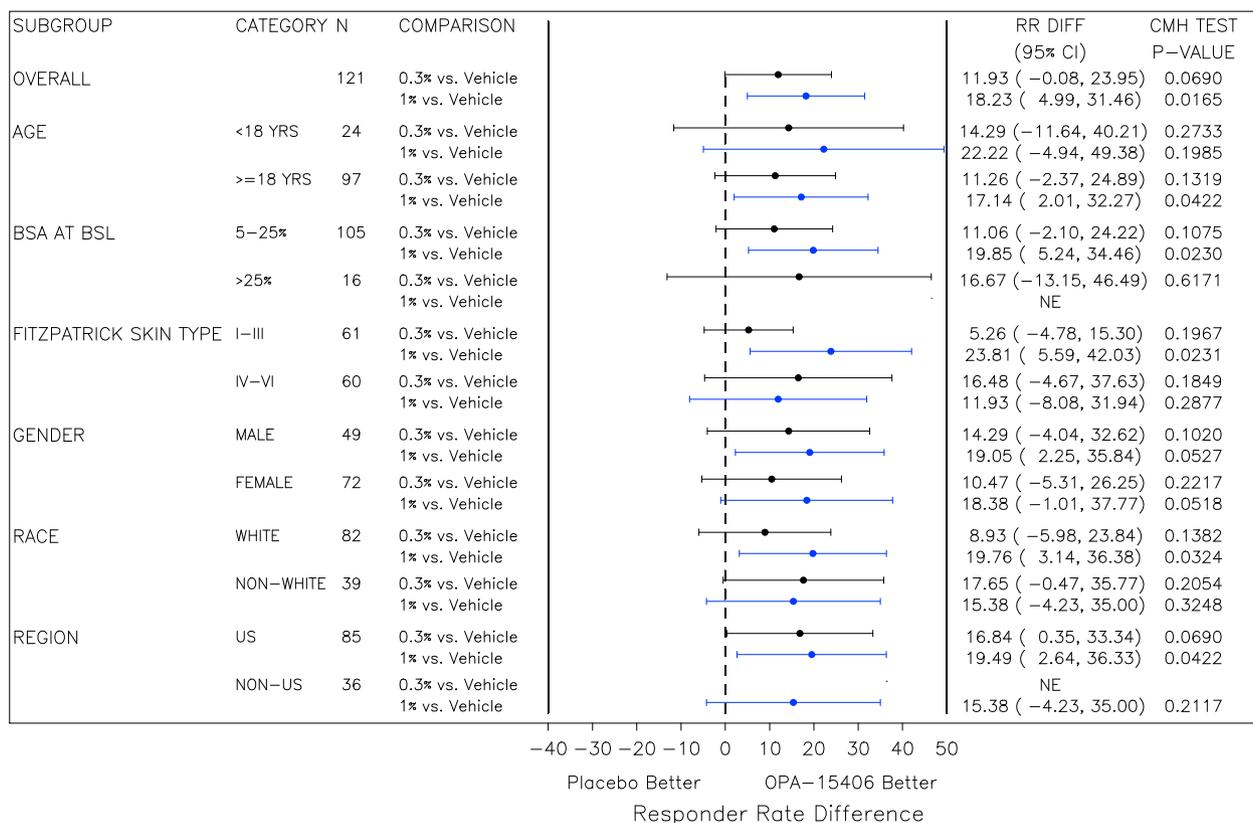


Fig 3. Subgroup analysis of success rate. Shown are the rates (plus 95% confidence intervals [CI]) at which patients received a score of 0 or 1 and had at least a 2-grade reduction from baseline (BSL) score within the designated subgroups at week 4. BSA, Body surface area; CMH, Cochran-Mantel-Haenszel; IGA, Investigator Global Assessment of Disease Severity; NE, not estimable; RR, responder rate.

group (Fig 5, A). The mean VAS pruritus scores improved from moderate (63.7 ± 20.3 mm) to mild (40.5 ± 27.1 mm) within 1 week, representing a 36.4% change from baseline. Improvements in pruritus were less dramatic in the OPA-15406 0.3% group. Change from baseline in response to question 1 of the DLQI/Children's DLQI, ie, "How itchy, scratchy and painful has your skin been over the last week?" also demonstrated statistically significant improvement ($P = .0082$) in patients treated with OPA-15406 1% by week 1. Overall, therapy with OPA-15406 1% resulted in early improvements in total quality-of-life scores by week 1 ($P = .0037$ vs vehicle) (Fig 5, B), representing a 37.2% change from baseline.

Pharmacokinetic analyses

Among the 9 patients with pharmacokinetics the percentage of overall BSA treated ranged from 5% to 33%; 1 of the 9 had more than 25% of BSA treated. After topical application, plasma levels of OPA-15406 were low for both the 0.3% and the 1% formulations on the first day of dosing, as

demonstrated by low maximum plasma concentration after administration (3.18 and 4.74 ng/mL, respectively) and area under the curve values (16.0 and 20.7 ng*h/mL, respectively) (Table II). Pharmacokinetic parameters at week 4 were similar to those on day 1, indicating no apparent accumulation of active drug after multiple twice-daily administrations of OPA-15406.

Tolerability

Of the 121 patients enrolled in this study, 62 (51%) experienced adverse events (18 of 43 [42%] in the OPA-15406 1% group, 24 of 41 [59%] in the OPA-15406 0.3% group, and 20 of 37 [54%] in the vehicle group). Of these, 11 (9%) patients experienced adverse events considered by the investigator to be at least potentially related to the study treatment (1 of 43 [2%] in the OPA-15406 1% group, 5 of 41 [12%] in the OPA-15406 0.3% group, and 5 of 37 [14%] in the vehicle group).

In all, 26 patients exhibited worsening of their AD, making this the most frequent adverse event in each treatment group (Table III). The worsening occurred

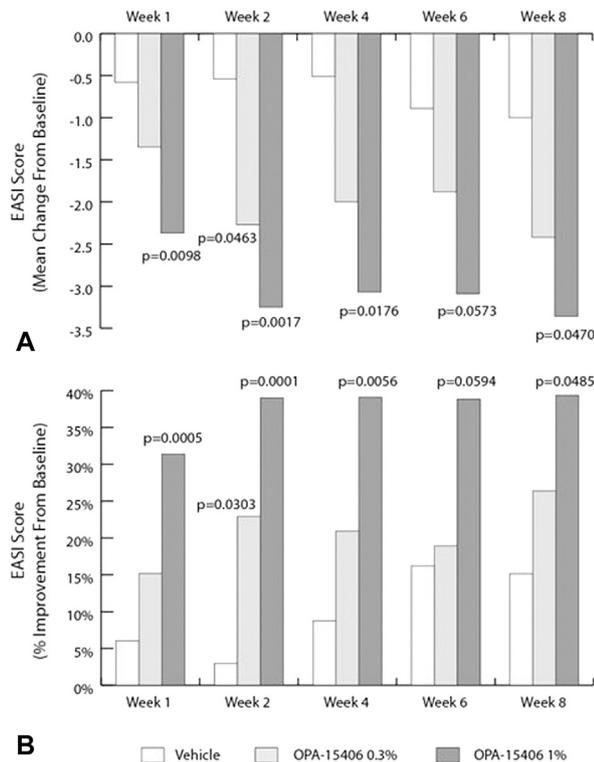


Fig 4. Clinician-reported outcomes based on the Eczema Area and Severity Index (EASI). **A**, Numeric least squares mean change from baseline in EASI score. **B**, Percentage improvement from baseline EASI score. *P* values are for comparisons with vehicle. Last observation carried forward was used to impute missing data.

in treated areas in 13 of the 26 patients (2 of 43 [5%] in the OPA-15406 1% group, 8 of 41 [20%] in the OPA-15406 0.3% group, and 3 of 37 [8%] in the vehicle group). In 5 patients, the worsening of AD was assessed as potentially treatment-related (recorded 3 times in the OPA-15406 0.3% group and 3 times in vehicle group); notably, none of the cases of treatment-related worsening of AD were reported in the OPA-15406 1% group.

The remaining treatment-related adverse events were yeast infection in 1 patient in the OPA-15406 1% group (study verbatim: vulvovaginal mycotic infection) and 1 case each of application site pain, erythema, and pruritus in the OPA-15406 0.3% group and application site irritation and pruritus in the vehicle group. All treatment-related adverse events were mild to moderate in intensity.

Five adverse events were classified as serious; none were related to study medication. In the OPA-15406 0.3% group, there was 1 newly diagnosed case of multiple sclerosis in a patient with family history of multiple sclerosis, and 1 case of abnormal liver function test results (meeting Hy law criteria) in a patient after acetaminophen/codeine

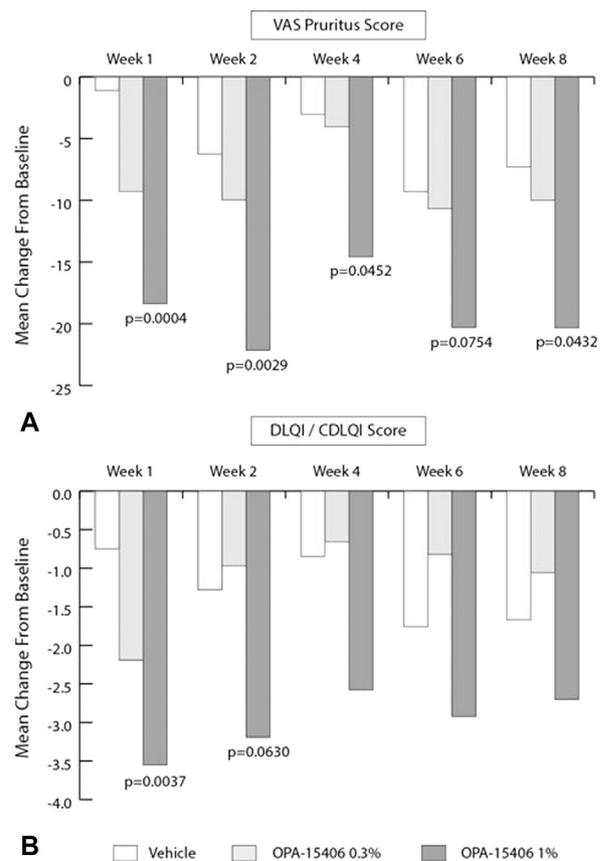


Fig 5. Patient-reported outcomes. **A**, Mean change from baseline in visual analog scale (VAS) pruritus scores per visit. **B**, Mean change from baseline in Dermatology Life Quality Index (DLQI) and the Children's DLQI (CDLQI) per visit. Values on both graphs are least squares means. *P* values are for comparisons with vehicle. Last observation carried forward was used to impute missing data.

combination therapy for tooth extraction pain. In the OPA-15406 1% group, 1 case each of worsening of depression, giardiasis infection, and splenic rupture caused by a motor accident was reported.

DISCUSSION

In this study, the PDE4 inhibitor OPA-15406, applied topically as a 0.3% (wt/wt) or 1% (wt/wt) ointment, provided therapeutic benefit to patients with mild to moderate AD. The benefit was documented by clinician-reported outcomes, including success rate (based on IGA score) and percentage change on the EASI score. OPA-15406 treatment was also associated with improvements in patient-reported outcomes, notably improvements in VAS pruritus scores, with significant treatment effects observed for the 1% formulation relative to vehicle at most time points in the study. Pruritus, a hallmark of AD, can lead to skin damage by

Table II. Pharmacokinetics

	OPA-15406 0.3%	OPA-15406 1%
Day 1		
N	4	4
C_{max} , ng/mL (SD)	3.18 (2.79)	4.74 (5.51)
t_{max} , median h (minimum, maximum)	4.01 (2.00, 4.07)	4.06 (4.00, 7.50)
AUC_{0-8hr} , ng*h/mL (SD)	16.0 (13.6)	20.7 (22.5)
Week 4		
N	5	4
C_{max} , ng/mL (SD)	2.94 (2.98)	1.38 (0.554)
t_{max} , median h (minimum, maximum)	4.15 (0, 8.00)	4.98 (0, 8.00)
AUC_{0-8hr} , ng*h/mL (SD)	20.1 (22.3)	8.58 (3.35)

Plasma samples were collected from a subset of patients on days 1 and 29 (week-4 visit) and subjected to pharmacokinetic analysis (see "Methods" section).

AUC_{0-8hr} , Area under the concentration curve from 0-8 hours; C_{max} , maximum plasma concentration after administration; t_{max} , time to reach C_{max} .

Table III. Tolerability

	OPA-15406 0.3%, N = 41 n (%)	OPA-15406 1%, N = 43 n (%)	Vehicle, N = 37 n (%)
Worsening atopic dermatitis	11 (26.8)	7 (16.3)	8 (21.6)
Nasopharyngitis	3 (7.3)	1 (2.3)	3 (8.1)
Headache	2 (4.9)	3 (7.0)	0 (0.0)
Worsening pruritus	3 (7.3)	0 (0.0)	1 (2.7)
Upper respiratory tract infection	3 (7.3)	1 (2.3)	0 (0.0)
Vomiting	0 (0.0)	2 (4.7)	1 (2.7)
Toothache	0 (0.0)	1 (2.3)	2 (5.4)
Impetigo	0 (0.0)	2 (4.7)	0 (0.0)
Diarrhea	0 (0.0)	2 (4.7)	0 (0.0)
Excoriation	0 (0.0)	0 (0.0)	2 (5.4)

Includes treatment-related and -unrelated adverse events occurring in $\geq 4\%$ of patients in any treatment group.

excoriation and the development of secondary infection, which further aggravates the disease.²⁹ Nocturnal scratching is one of the most common symptoms of AD and often results in sleep disturbances and dramatic impairment in quality of life, especially in children. Thus, a new treatment modality with a direct positive impact on limiting pruritus, while simultaneously decreasing inflammation in affected skin, has the potential to substantially improve therapeutic options for the management of AD.

Several other features of OPA-15406 therapy were noted in this study. First, the anti-inflammatory and antipruritic effects had rapid onset, with statistically significant differences from vehicle in some parameters within 1 week of treatment. In general, the positive effects of OPA-15406 were sustained through the week-8 visit, but the differences between active and vehicle arms diminished slightly as skin condition improved in the vehicle group over time, presumably as a result of the emollients in the ointment base. Second, in all assessments, OPA-15406 1% exhibited better clinical and patient-reported outcomes than OPA-15406 0.3%, suggesting a clear dose response. Finally, the nature and number of treatment-related adverse events, combined with the negligible systemic exposure after OPA-15406 application, indicated an overall favorable tolerability profile for this new topical agent.

Our study has limitations because of the compound's early developmental stage, eg, the relatively small number of enrolled patients, and it is difficult to predict how OPA-15406 will compare with topical calcineurin inhibitors, topical corticosteroids, or other PDE4 inhibitors. Moreover, further investigations in pediatric patient populations (age <10 years) will be needed. Nonetheless, the consistent and beneficial effects observed in this study support further evaluation of OPA-15406 1% ointment for the treatment of AD in large randomized phase-III trials.

The authors thank Peter Loonan, Yanlin Wang, and William J. Brock (OPDC Programming, Pharmacokinetics, and Nonclinical, respectively); Hidetaka Hiyama and the Ako Research Institute in Japan and Otsuka Pharmaceutical Co Ltd in Japan; and the investigators, research staff, and patients in the United States, Poland, and Australia who contributed to the data and support of this study. The authors also thank David Norris, PhD (Ecosse Medical Communications, Falmouth, MA) for editorial assistance provided during the preparation of this report.

REFERENCES

- International Conference on Harmonization. ICH harmonised tripartite guideline. Guideline for good clinical practice. E6(R1). Current Step 4 version. Available from: URL: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf. Dated June 10, 1996.
- World Medical Association. Declaration of Helsinki - ethical principles for medical research involving human subjects. Available from: URL: <http://www.wma.net/en/30publications/10policies/b3/>. Accessed June 13, 2015.
- Berke R, Singh A, Guralnick M. Atopic dermatitis: an overview. *Am Fam Physician*. 2012;86(1):35-42.
- Hanifin JM, Cooper KD, Ho VC, et al. Guidelines of care for atopic dermatitis, developed in accordance with the American

- Academy of Dermatology (AAD)/American Academy of Dermatology Association "Administrative Regulations for Evidence-Based Clinical Practice Guidelines". *J Am Acad Dermatol*. 2004;50(3):391-404.
5. Kay J, Gawkrödger DJ, Mortimer MJ, Jaron AG. The prevalence of childhood atopic eczema in a general population. *J Am Acad Dermatol*. 1994;30(1):35-39.
 6. Perkin MR, Strachan DP, Williams HC, Kennedy CT, Golding J, Team AS. Natural history of atopic dermatitis and its relationship to serum total immunoglobulin E in a population-based birth cohort study. *Pediatr Allergy Immunol*. 2004;15(3):221-229.
 7. Ellis CN, Mancini AJ, Paller AS, Simpson EL, Eichenfield LF. Understanding and managing atopic dermatitis in adult patients. *Semin Cutan Med Surg*. 2012;31(3 Suppl):S18-S22.
 8. Hanifin JM, Reed ML. A population-based survey of eczema prevalence in the United States. *Dermatitis*. 2007;18(2):82-91.
 9. Hoare C, Li Wan Po A, Williams H. Systematic review of treatments for atopic eczema. *Health Technol Assess*. 2000;4(37):1-191.
 10. El-Batawy MM, Bosseila MA, Mashaly HM, Hafez VS. Topical calcineurin inhibitors in atopic dermatitis: a systematic review and meta-analysis. *J Dermatol Sci*. 2009;54(2):76-87.
 11. Schram ME, Roekevisch E, Leeflang MM, Bos JD, Schmitt J, Spuls PI. A randomized trial of methotrexate versus azathioprine for severe atopic eczema. *J Allergy Clin Immunol*. 2011;128(2):353-359.
 12. Haeck IM, Knol MJ, Ten Berge O, van Velsen SG, de Bruin-Weller MS, Bruijnzeel-Koomen CA. Enteric-coated mycophenolate sodium versus cyclosporin A as long-term treatment in adult patients with severe atopic dermatitis: a randomized controlled trial. *J Am Acad Dermatol*. 2011;64(6):1074-1084.
 13. Schmitt J, Schakel K, Folster-Holst R, et al. Prednisolone vs cyclosporin for severe adult eczema. An investigator-initiated double-blind placebo-controlled multicenter trial. *Br J Dermatol*. 2010;162(3):661-668.
 14. Dhar S, Seth J, Parikh D. Systemic side-effects of topical corticosteroids. *Indian J Dermatol*. 2014;59(5):460-464.
 15. *Protopic [package insert]*. Deerfield, IL: Astellas Pharma US Inc; 2010.
 16. *Elidel [package insert]*. Bridgewater, NJ: Valeant Pharmaceuticals North America LLC; 2014.
 17. Margolis DJ, Abuabara K, Hoffstad OJ, Wan J, Raimondo D, Bilker WB. Association between malignancy and topical use of pimecrolimus. *JAMA Dermatol*. 2015;151(6):594-599.
 18. Legendre L, Barnetche T, Mazereeuw-Hautier J, Meyer N, Murrell D, Paul C. Risk of lymphoma in patients with atopic dermatitis and the role of topical treatment: a systematic review and meta-analysis. *J Am Acad Dermatol*. 2015;72(6):992-1002.
 19. Hanifin JM, Butler JM, Chan SC. Immunopharmacology of the atopic diseases. *J Invest Dermatol*. 1985;85(1 Suppl):161s-164s.
 20. Furue M, Kitahara Y, Akama H, et al. Safety and efficacy of topical E6005, a phosphodiesterase 4 inhibitor, in Japanese adult patients with atopic dermatitis: results of a randomized, vehicle-controlled, multicenter clinical trial. *J Dermatol*. 2014;41(7):577-585.
 21. Baumer W, Hoppmann J, Rundfeldt C, Kietzmann M. Highly selective phosphodiesterase 4 inhibitors for the treatment of allergic skin diseases and psoriasis. *Inflamm Allergy Drug Targets*. 2007;6(1):17-26.
 22. Hanifin J, Rajka G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol Suppl*. 1980;92:44-47.
 23. Rajka G, Langeland T. Grading of the severity of atopic dermatitis. *Acta Derm Venereol Suppl (Stockh)*. 1989;144:13-14.
 24. Mosteller RD. Simplified calculation of body-surface area. *N Engl J Med*. 1987;317(17):1098.
 25. Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M. The Eczema Area and Severity Index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. *Exp Dermatol*. 2001;10(1):11-18.
 26. Phan NQ, Blome C, Fritz F, et al. Assessment of pruritus intensity: prospective study on validity and reliability of the visual analogue scale, numerical rating scale and verbal rating scale in 471 patients with chronic pruritus. *Acta Derm Venereol*. 2012;92(5):502-507.
 27. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)—a simple practical measure for routine clinical use. *Clin Exp Dermatol*. 1994;19(3):210-216.
 28. Lewis-Jones MS, Finlay AY. The Children's Dermatology Life Quality Index (CDLQI): initial validation and practical use. *Br J Dermatol*. 1995;132(6):942-949.
 29. Hong J, Buddenkotte J, Berger TG, Steinhoff M. Management of itch in atopic dermatitis. *Semin Cutan Med Surg*. 2011;30(2):71-86.