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ORIGINAL ARTICLE

Efficacy and safety of topical OPA-15406, a new phosphodiesterase 4 inhibitor, in Japanese patients with atopic dermatitis for 8 weeks: A phase 2, randomized, double-blind, placebo-controlled study

Hidehisa SAEKI,[1] Makoto KAWASHIMA,[2,*] Satoko SUGAYA,[3] Kazuhide OSHIDEN,[4] Hidetsugu TSUBOUCHI[5]

[1]*Department of Dermatology, Nippon Medical School,* [2]*Department of Dermatology, Tokyo Women's Medical University,* [3]*Headquarters of Clinical Development, Otsuka Pharmaceutical Co., Ltd, Tokyo,* [4]*Headquarters of Clinical Development,* [5]*Medical Affairs, Otsuka Pharmaceutical Co., Ltd, Osaka, Japan*

ABSTRACT

The efficacy and safety of topical OPA-15406, a new phosphodiesterase 4 inhibitor, were examined in Japanese patients aged 15–70 years with atopic dermatitis in a phase 2, randomized, double-blind, vehicle-controlled study. Two hundred patients were randomized to three treatment groups at a 1:1:1 ratio to receive OPA-15406 0.3%, OPA-15406 1% or vehicle ointment twice daily for 8 weeks. The OPA-15406 1% group was superior to the vehicle group in terms of the incidence of success based on the Investigator Global Assessment score at week 4 (P = 0.0328), which was the primary end-point, while the OPA-15406 0.3% group showed a trend toward improvement in the primary end-point. The mean Eczema Area and Severity Index total score and subscale (erythema, induration/papulation, excoriation and lichenification) scores, the Visual Analog Scale pruritus score and the Patient-Oriented Eczema Measure score were significantly improved and the percentage of affected body surface area was significantly decreased in both OPA-15406 groups relative to the vehicle group as early as week 1, and the improved scores and decreased percentages were generally maintained until week 8. No deaths or serious treatment-emergent adverse events occurred in the OPA-15406 treatment groups. Treatment-emergent adverse events frequently observed across treatment groups were worsening of atopic dermatitis, viral upper respiratory tract infection and pruritus, all of which were mild or moderate in severity in the OPA-15406 groups. OPA-15406 1% ointment showed favorable efficacy and safety profiles, indicating a promising treatment option for patients with atopic dermatitis.

Key words: **atopic dermatitis, OPA-15406, phosphodiesterase 4 inhibitor, pruritus, topical.**

INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by pruritus, dry skin and relapsing dermatitis. It occurs more commonly in young individuals, with the prevalence ranging 10–25% in children and 2–10% in adults in developed countries.[1]

Atopic dermatitis is associated with pruritus, leading to sleep disturbance and functional impairment, and secondary consequences, including neuropsychiatric symptoms (anxiety and depression) and reduced health-related quality of life.[2] Pruritus, a hallmark of AD, can lead to skin damage as patients may scratch until bleeding excoriations result, which further aggravates the disease.[3] Furthermore, AD is primarily a chronic, relapsing and lifelong condition for patients, and causes a substantial economic burden in addition to the disease burden.[4] In 2014, the total number of patients with AD receiving treatment in Japan was estimated to be 456 000 according to the figures reported by the Ministry of Health, Labor and Welfare.[5]

The complicated interaction among genetics, environmental factors, impaired skin barrier and immunological abnormality probably contributes to the development of AD.[6] Considering such a complex pathogenesis, AD treatment is currently aimed at symptomatic control rather than cure. Therefore, the principal goal of AD treatment is to reach and maintain a state of

Correspondence: Hidetsugu Tsubouchi, Ph.D., Medical Affairs, Otsuka Pharmaceutical Co., Ltd, 3-2-27 Otedori, Chuo-ku, Osaka 540-0021, Japan. Email: tsubouchi.hidetsugu@otsuka.jp
*Present address: Tokyo Men's Health Clinic, Tokyo, Japan.
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absent or minor clinical symptoms that do not disturb the patients' daily activities.[7]

Topical emollients, which repair skin barrier function and prevent penetration of irritants, are first-line agents for the treatment of AD. The benefit of topical corticosteroids (TCS) is well recognized, and pharmacotherapy with TCS is initiated as first-line treatment for patients with acute flares.[1,8] Tacrolimus, a topical calcineurin inhibitor, is a steroid-sparing topical agent and is deemed as a second-line agent following TCS.[8–10]

OPA-15406 is a new phosphodiesterase 4 (PDE4) inhibitor developed by Otsuka Pharmaceutical (Tokyo, Japan). PDE4 releases pro-inflammatory cytokines by the degradation of cyclic adenosine monophosphate and is associated with the pathogenesis of inflammatory disorders.[11] Studies have shown increased PDE4 activity in the inflammatory cells of AD patients.[11,12] Thus, PDE4 inhibition has been considered to be a therapeutic target for AD.[1] In a previous phase 2 clinical study conducted in Australia, Poland and the USA, OPA-15406 1% ointment provided beneficial therapeutic effects with a low incidence of adverse events (AE) in AD patients.[13] Based on the results of the afore-mentioned study, we designed a phase 2, randomized, double-blind, vehicle-controlled study to assess the efficacy and safety of OPA-15406 0.3% and 1% ointments applied twice daily for 8 weeks in Japanese patients with AD.

METHODS

This study was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline and the applicable local laws and regulatory requirements in Japan. The protocol was reviewed and approved by the governing institutional review board for each study site and conformed to the provisions of the Declaration of Helsinki. Written informed consent was obtained from all patients prior to initiation of any study-related procedures. If a patient was under 20 years of age, written informed consent was obtained from both the patient and the patient's legal guardian.

Patients

Male and female outpatients aged between 15 and 70 years who were diagnosed with AD according to the Hanifin and Rajka criteria[14] and had at least a 3-year history of the disease were eligible for inclusion in the study. Patients were required to have a baseline Investigator Global Assessment (IGA) score[15] of 2 (mild) or 3 (moderate) and an AD-affected body surface area (BSA)[16] of at least 5% but not more than 40%.

Patients with a clinically significant complication or history of any disorder and those with a clinically significant abnormal laboratory test value, blood pressure and pulse rate result, or electrocardiogram (ECG) finding were excluded. Patients who could not stop using TCS, immunomodulators, retinoids or antihistamines from 7 days before the baseline examination; those who could not stop using systemic corticosteroids, immunomodulators, antimetabolites, retinoids or biologics from 28 days before the baseline examination; those who could not stop using ultraviolet phototherapy from 28 days before the baseline examination; or those who could not stop using systemic antihistamines, sodium cromoglicate, tranilast or suplatast tosilate from 7 days before the baseline examination were excluded. Female patients who were pregnant or breast-feeding or did not agree to birth control were also excluded.

Study design

This phase 2 study was conducted at 14 study sites in Japan between September 2016 and June 2017 (Clinical Trials.gov identifier: NCT02914548). The study consisted of a screening period (2–30 days), a treatment period (8 weeks) and a post-treatment observation period (2 weeks). The screening period was defined as the period between the day of the screening examination and the day of the baseline examination. Patients who met the inclusion criteria and did not meet any of the exclusion criteria at the baseline examination proceeded to the treatment period, which was defined as the period between the day of the baseline examination and the day of the week 8 examination (or the day of discontinuation).

Patients could discontinue participation in the study for any reason, without any medical disadvantage. If a patient discontinued participation during the treatment period, the examination at the time of discontinuation was performed for the patient.

Eligible patients were randomized to one of the three investigational medicinal product (IMP) treatment groups at a 1:1:1 ratio to receive OPA-15406 0.3% (w/w), OPA-15406 1% (w/w) or vehicle ointment by using a blinded dynamic allocation. Allocated patients received the respective IMP twice daily, approximately 12 h apart, between the morning application and night application for 8 weeks. The IMP allocation manager prepared a randomization table for setting the interactive web response system. The vehicle ointment was identical in appearance to the OPA-15406 ointments.

Patients were instructed to apply the IMP to the treatment area. The treatment area was defined as the affected BSA at baseline. If the affected BSA expanded after the baseline examination, the expanded area was also included in the treatment area. The patient's total BSA was calculated based on height and bodyweight at the screening examination using Mosteller's formula.[16] The dose for each patient was calculated using the following formula: IMP amount applied to 1% of the total BSA (g) × percentage of affected BSA (%). The IMP amount applied to 1% of the total BSA for each patient was as follows: 0.1 g for total BSA of less than 1.0 m^2, 0.15 g for total BSA of 1.0 m^2 or more and less than 1.3 m^2, 0.2 g for total BSA of 1.3 m^2 or more and less than 1.6 m^2, 0.25 g for total BSA of 1.6 m^2 or more and less than 1.9 m^2, and 0.3 g for total BSA of 1.9 m^2 or more.

Efficacy assessments

The primary end-point was the incidence of success at week 4 in the IGA score.[15] The incidence of success in the IGA score was defined as the percentage of responders who had a score of 0 or 1 along with at least a 2-grade reduction from baseline. The IGA score was evaluated using a 5-point scale (0, clear; 1, almost clear; 2, mild; 3, moderate; 4, severe/very severe).[15]

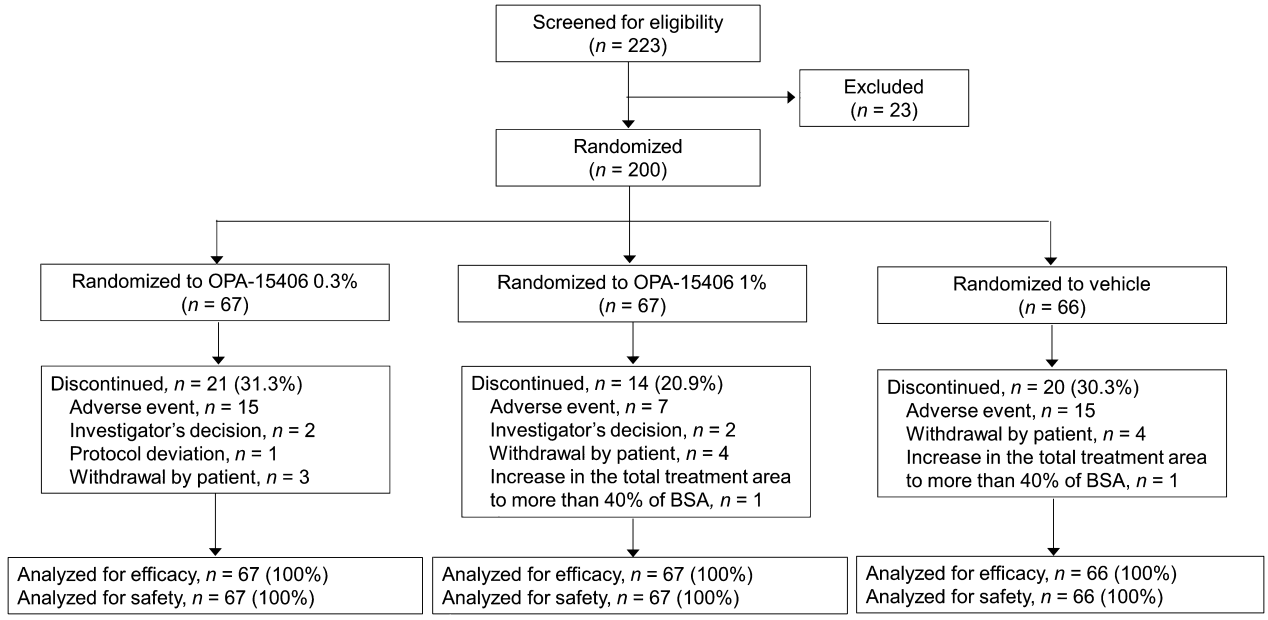

Figure 1. Patient disposition. BSA, body surface area.

Table 1. Demographic and clinical characteristics

	OPA-15406 0.3% (*n* = 67)	OPA-15406 1% (*n* = 67)	Vehicle (*n* = 66)
Age, years, mean ± SD	30.2 ± 9.0	31.0 ± 10.8	31.6 ± 10.0
Male, *n* (%)	45 (67.2)	42 (62.7)	43 (65.2)
Weight, kg, mean ± SD	62.2 ± 11.6	62.5 ± 11.3	66.2 ± 13.8
Height, cm, mean ± SD	166.8 ± 8.6	166.0 ± 8.1	166.5 ± 9.2
BMI, kg/m^2, mean ± SD	22.2 ± 3.0	22.6 ± 3.6	23.8 ± 4.2
AD duration, years, mean ± SD	25.1 ± 11.0	24.4 ± 10.6	25.2 ± 9.2
IGA score, *n* (%)			
Mild disease	19 (28.4)	19 (28.4)	19 (28.8)
Moderate disease	48 (71.6)	48 (71.6)	47 (71.2)
EASI score, mean ± SD	9.91 ± 5.29	9.38 ± 5.07	9.08 ± 5.26
VAS pruritus score, mean ± SD	51.4 ± 24.4	51.1 ± 24.2	51.7 ± 24.5
POEM score, mean ± SD	12.8 ± 6.3	13.1 ± 5.9	11.8 ± 6.2
DLQI score, mean ± SD	6.4 ± 5.2	5.6 ± 3.7	6.1 ± 4.8
Affected BSA, *n* (%)			
≥5% to <10%	5 (7.5)	8 (11.9)	12 (18.2)
≥10% to <30%	51 (76.1)	50 (74.6)	43 (65.2)
≥30%	11 (16.4)	9 (13.4)	11 (16.7)

Data are expressed as number (%) or mean ± SD. AD, atopic dermatitis; BMI, body mass index; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; POEM, Patient-Oriented Eczema Measure; SD, standard deviation; VAS, Visual Analog Scale.

The secondary end-points included the incidence of success in the IGA score at weeks 1 and 8. Secondary end-points also included the changes from baseline at weeks 1, 4 and 8 in the IGA score, in the Eczema Area and Severity Index (EASI) score and each subscale (erythema, induration/papulation, excoriation and lichenification) score,[17] in the Visual Analog Scale (VAS) pruritus score,[18] in the Patient-Oriented Eczema Measure (POEM) score,[19] in the Dermatology Life Quality Index (DLQI) score[20] and in the percentage of affected BSA.

Pharmacokinetics

Pharmacokinetic (PK) analyses of OPA-15406 included the mean maximum plasma concentration (C_{max}, ng/mL) and the

mean area under the plasma concentration–time curve from time 0 to 8 h ($AUC_{8\ h}$, ng•h/mL) on day 1 and at week 4. For these analyses, blood samples were collected prior to initiation of the IMP application and 2, 4 and 8 h post-dose on day 1 and at week 4. PK analysis also included the mean normalized plasma trough concentration before application at weeks 1, 4 and 8, which was normalized by the dose derived from the percentage of the affected BSA.

On the day of blood collection, patients visited the study sites without the morning IMP application. Plasma concentration of OPA-15406 was quantified by using liquid chromatography with tandem mass spectrometry at LSI Medience (Tokyo, Japan).

Safety assessments

Safety assessments included observation of treatment-emergent AE (TEAE), clinical laboratory tests (hematology, serum chemistry and qualitative urinalysis), physical examinations, vital sign assessments (body temperature, blood pressure, pulse rate and bodyweight) and 12-lead ECG examination. TEAE were categorized according to the Medical Dictionary for Regulatory Activities (MedDRA)/J version 20.0. The severity of the TEAE was classified as mild, moderate and severe. The causal relationship with the IMP was assessed as "not related" or "related".

Statistical analysis

The efficacy and safety datasets included all patients who received any IMP at least once. For the primary end-point, patients with missing data for the IGA score at scheduled visits were considered as non-responders for that visit.

For the primary end-point of the incidence of success in the IGA score at week 4, a comparison between the OPA-15406 1% group and the vehicle group was first performed. If a significant effect was found for the OPA-15406 1% group with a two-sided significance level of 0.05, a comparison between the OPA-15406 0.3% group and the vehicle group was then performed. The Cochran–Mantel–Haenszel test was performed using the baseline IGA score as a stratification factor. The difference in the incidence of success in the IGA score and its two-sided 95% confidence interval (CI) were determined. For the revised responder analysis, patients who achieved an IGA score of 0 or 1 without at least a 2-grade reduction from baseline at week 4 were counted as responders. The analysis method for the secondary end-point of the incidence of success in the IGA score at weeks 1 and 8 was the same as that used for the primary end-point.

For the change from baseline in the IGA score as the secondary end-point, a mixed-model repeated measures analysis with an unstructured error covariance matrix was performed. The standard error was calculated by the Kenward–Roger method. The least square (LS) mean was calculated by treatment group and by time point. The difference in the LS means between each OPA-15406 group and the vehicle group, the two-sided 95% CI and the *P*-value were calculated. The other secondary end-points were analyzed by the same method as that used for the change from baseline in the IGA score. For reference data, the incidence of success in the IGA score, and the changes from baseline in the IGA score, in the EASI score and the subscale scores, in the VAS pruritus score, in the POEM score, in the DLQI score and in the percentage of affected BSA were analyzed at weeks 2 and 6 by using the same methods as those used at weeks 1, 4 and 8.

RESULTS

Patients

Of the 223 patients screened, 200 patients were randomized to the double-blind treatment: 67 to the OPA-15406 0.3% group, 67 to the OPA-15406 1% group and 66 to the vehicle group. Overall, 145 patients (72.5%) completed the study. The completion rates in the OPA-15406 0.3%, OPA-15406 1% and vehicle groups were 68.7% (46/67), 79.1% (53/67) and 69.7% (46/66), respectively. The most frequently reported reasons for discontinuation across all treatment groups were AE (18.5%) and withdrawal by patient (5.5%) (Fig. 1).

Demographic and clinical characteristics of the patients are shown in Table 1. The majority of the randomized patients were male (65.0%). The overall mean age was 30.9 ± 9.9 years. In total, 57 patients (28.5%) had an IGA score of 2 and 143 (71.5%) had an IGA score of 3. The overall mean duration since onset of AD was 24.9 ± 10.3 years. The baseline EASI, VAS pruritus, POEM and DLQI scores were similar across treatment groups.

Efficacy

The incidences of success in the IGA score at week 4 as the primary end-point were 14.93% (95% CI, 7.40–25.74) for the OPA-15406 0.3% group, 22.39% (95% CI, 13.11–34.22) for the OPA-15406 1% group and 9.09% (95% CI, 3.41–18.74) for the vehicle group. The incidence of success in the IGA score at week 4, which was the primary end-point, was significantly greater in the OPA-15406 1% group compared with the vehicle

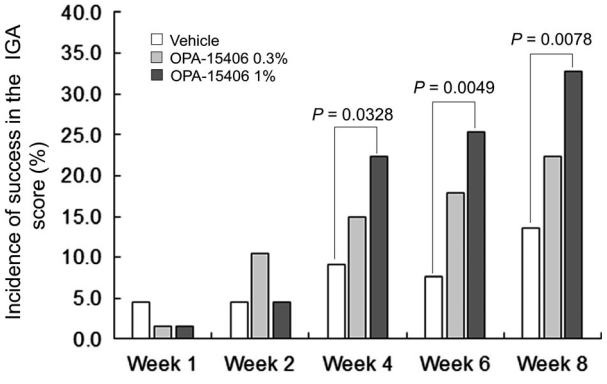

Figure 2. Incidence of success in the IGA score at each time point. Overall, 66, 67 and 67 patients were evaluated in the vehicle, OPA-15406 0.3% and OPA-15406 1% groups, respectively, at all time points. *P*-values are for the comparison between each OPA-15406 group and the vehicle group. IGA, Investigator Global Assessment.

Table 2. Summary of LS mean changes from baseline in efficacy parameters

	OPA-15406 0.3%			OPA-15406 1%			Vehicle	
	Mean (SE)	*n*	*P*	Mean (SE)	*n*	*P*	Mean (SE)	*n*
IGA								
Week 1	−0.32 (0.07)	67	0.0836	−0.38 (0.07)	67	0.0208	−0.14 (0.07)	66
2	−0.45 (0.09)	63	0.0761	−0.47 (0.09)	64	0.0553	−0.22 (0.09)	57
4	−0.55 (0.12)	57	0.0782	−0.73 (0.11)	58	0.0050	−0.26 (0.12)	53
6	−0.64 (0.12)	49	0.1268	−0.92 (0.12)	54	0.0020	−0.37 (0.13)	49
8	−0.72 (0.13)	47	0.8064	−1.01 (0.13)	53	0.0758	−0.68 (0.13)	46
EASI								
Week 1	−1.94 (0.52)	67	0.0003	−2.73 (0.52)	67	<0.0001	0.75 (0.52)	66
2	−2.20 (0.66)	63	0.0161	−3.14 (0.65)	64	0.0008	0.11 (0.68)	57
4	−2.32 (0.75)	57	0.0470	−3.16 (0.75)	58	0.0062	−0.15 (0.77)	53
6	−2.61 (0.79)	49	0.0621	−3.64 (0.78)	54	0.0061	−0.47 (0.81)	49
8	−2.51 (0.87)	47	0.4102	−3.73 (0.85)	53	0.0723	−1.48 (0.89)	46
VAS pruritus								
Week 1	−12.52 (2.62)	67	0.0001	−14.08 (2.62)	67	<0.0001	2.07 (2.64)	66
2	−9.94 (2.69)	63	0.0016	−10.75 (2.67)	64	0.0008	2.45 (2.79)	57
4	−6.76 (3.21)	57	0.0986	−6.28 (3.19)	58	0.1204	0.90 (3.31)	53
6	−4.35 (3.32)	49	0.1900	−9.68 (3.24)	54	0.0147	1.89 (3.38)	49
8	−4.46 (3.29)	47	0.8232	−9.15 (3.17)	53	0.2136	−3.41 (3.33)	46
POEM								
Week 1	−2.75 (0.58)	67	0.0186	−4.05 (0.58)	67	0.0001	−0.80 (0.58)	66
2	−2.69 (0.69)	63	0.0059	−3.48 (0.69)	64	0.0004	0.07 (0.71)	57
4	−1.36 (0.77)	57	0.2232	−2.90 (0.76)	58	0.0095	−0.02 (0.79)	53
6	−0.89 (0.81)	49	0.9069	−3.01 (0.79)	54	0.0509	−0.76 (0.82)	49
8	−0.82 (0.83)	47	0.9958	−2.60 (0.81)	53	0.1319	−0.83 (0.84)	46
DLQI								
Week 1	−0.91 (0.43)	67	0.1140	−1.57 (0.43)	67	0.0082	0.06 (0.43)	66
2	−0.90 (0.54)	63	0.0928	−0.80 (0.54)	64	0.1180	0.41 (0.56)	57
4	0.23 (0.62)	57	0.8413	0.26 (0.61)	58	0.8683	0.41 (0.63)	53
6	0.34 (0.62)	49	0.5652	0.42 (0.61)	54	0.5030	−0.18 (0.64)	49
8	0.24 (0.62)	47	0.5362	−0.12 (0.60)	53	0.8273	−0.31 (0.63)	46
Affected BSA								
Week 1	−2.90 (0.97)	67	0.0014	−3.19 (0.96)	67	0.0007	1.53 (0.97)	66
2	−3.82 (1.22)	63	0.0275	−3.51 (1.21)	64	0.0421	0.05 (1.25)	57
4	−3.94 (1.44)	57	0.0817	−3.73 (1.43)	58	0.0993	−0.32 (1.48)	53
6	−4.44 (1.45)	49	0.0748	−5.27 (1.43)	54	0.0291	−0.72 (1.48)	49
8	−4.14 (1.53)	47	0.2478	−6.32 (1.50)	53	0.0315	−1.60 (1.56)	46

Data are expressed as mean (SE). BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; LS, least squares; POEM, Patient-Oriented Eczema Measure; SE, standard error; VAS, Visual Analog Scale.

group (difference: 13.22%; 95% CI, 1.36–25.07; $P = 0.0328$), while the OPA-15406 0.3% group showed a trend toward improvement in the primary end-point (Fig. 2). Furthermore, based on the revised responder analysis, the incidences of success at week 4 were 26.87% (difference vs vehicle: 14.80%; 95% CI, 1.52–28.08; $P = 0.0309$) for the OPA-15406 0.3% group, 32.84% (difference vs vehicle: 20.74%; 95% CI, 6.98–34.49; $P = 0.0045$) for the OPA-15406 1% group and 12.12% for the vehicle group.

For the secondary end-points, the incidence of success in the IGA score was significantly greater in the OPA-15406 1% group relative to the vehicle group at week 8 (difference: 19.11%; 95% CI, 5.45–32.76; $P = 0.0078$) (Fig. 2).

The LS mean changes from baseline in the IGA, EASI, VAS pruritus, POEM and DLQI scores and in the percentage of affected BSA are presented in Table 2. A significant difference between the OPA-15406 1% and vehicle groups for decrease in the IGA score was observed at week 1 (difference: −0.24; 95% CI, −0.43 to −0.04; $P = 0.0208$) and at week 4 (difference: −0.47; 95% CI, −0.80 to −0.14; $P = 0.0050$). Both OPA-15406 groups showed a significant decrease at week 1 in the EASI, VAS pruritus and POEM scores compared with the vehicle group, and the improved scores were generally maintained until week 8. A significant LS mean change from baseline relative to vehicle in the DLQI score was noted for the OPA-15406 1% group at week 1.

The LS mean changes from baseline in the subscale EASI scores (erythema, induration/papulation, excoriation and lichenification) are presented in Figure 3. Both OPA-15406 groups showed significant efficacy for these symptom scores

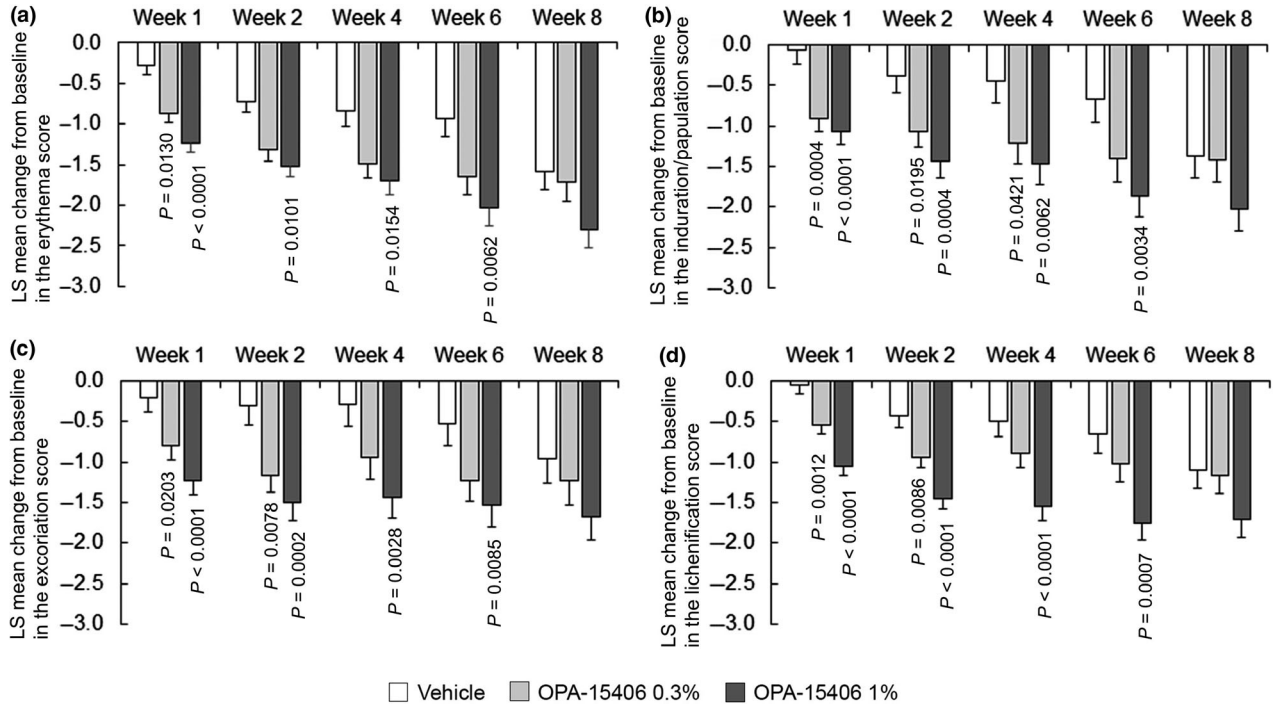

Figure 3. Least square (LS) mean change from baseline in the subscale scores of the Eczema Area and Severity Index at each time point: (a) erythema score; (b) induration/papulation score; (c) excoriation score; and (d) lichenification score. In the vehicle, OPA-15406 0.3% and OPA-15406 1% groups, 66, 67 and 67 patients, respectively, were evaluated at week 1; 57, 63 and 64 patients, respectively, were evaluated at week 2; 53, 57 and 58 patients, respectively, were evaluated at week 4; 49, 49 and 54 patients, respectively, were evaluated at week 6; and 46, 47 and 53 patients, respectively, were evaluated at week 8. *P*-values are for the comparison between each OPA-15406 group and the vehicle group.

Table 3. Mean maximum plasma concentration and mean area under the plasma concentration–time curve from time 0 to 8 h following topical application of OPA-15406 ointment

	OPA-15406 0.3%	OPA-15406 1%
Day 1	*n* = 11	*n* = 9
C_{max}, ng/mL, mean (SD)	4.01 (5.90)	7.27 (6.42)
$AUC_{8\ h}$, ng•h/mL, mean (SD)	22.0 (34.7)	41.6 (37.6)
Week 4	*n* = 8	*n* = 6
C_{max}, ng/mL, mean (SD)	2.07 (1.47)	10.4 (3.68)
$AUC_{8\ h}$, ng•h/mL, mean (SD)	11.6 (7.23)	65.2 (26.8)

Data are expressed as number or mean (SD). $AUC_{8\ h}$, area under the plasma concentration–time curve from time 0 to 8 h; C_{max}, maximum plasma concentration; *n*, number of non-missing observations; SD, standard deviation.

Table 4. Mean normalized plasma trough concentration following topical application of OPA-15406 ointment

Mean normalized plasma trough concentration	OPA-15406 0.3%	OPA-15406 1%
Week 1, ng/mL per mg, mean (SD)	0.114 (0.0991) [*n* = 53]	0.113 (0.0952) [*n* = 59]
Week 4, ng/mL per mg, mean (SD)	0.104 (0.119) [*n* = 49]	0.127 (0.119) [*n* = 50]
Week 8, ng/mL per mg, mean (SD)	0.0910 (0.103) [*n* = 43]	0.137 (0.242) [*n* = 46]

Data are expressed as number or mean (SD). *n*, number of non-missing observations; SD, standard deviation. Plasma trough concentration was normalized by the dose derived from the percentage of affected body surface area.

compared with the vehicle group as early as week 1, and the improved scores were sustained through week 8.

The LS mean percentage of affected BSA was significantly decreased in the OPA-15406 1% and 0.3% groups relative to the vehicle group at week 1, and the decreased percentages were maintained until week 8 (Table 2).

Pharmacokinetics

After topical application of OPA-15406 0.3% and 1% ointments, the mean C_{max} was 4.01 ± 5.90 and 7.27 ± 6.42 ng/mL, respectively, on day 1, and 2.07 ± 1.47 and 10.4 ± 3.68 ng/mL, respectively, at week 4. The mean $AUC_{8\ h}$ for the OPA-15406 0.3% and 1% groups was 22.0 ± 34.7 and 41.6 ± 37.6 ng•h/mL, respectively, on day 1, and 11.6 ± 7.23 and 65.2 ± 26.8 ng•h/mL, respectively, at week 4 (Table 3).

Table 5. Summary of treatment-emergent adverse events observed in at least 1% of patients in the total treatment groups

	OPA-15406 0.3% (*n* = 67)	OPA-15406 1% (*n* = 67)	Vehicle (*n* = 66)	Total (*n* = 200)
Gastrointestinal disorders, *n* (%)				
Diarrhea	1 (1.5)	1 (1.5)	0 (0.0)	2 (1.0)
Infections and infestations, *n* (%)				
Conjunctivitis	1 (1.5)	1 (1.5)	0 (0.0)	2 (1.0)
Folliculitis	1 (1.5)	1 (1.5)	0 (0.0)	2 (1.0)
Influenza	2 (3.0)	1 (1.5)	0 (0.0)	3 (1.5)
Viral upper respiratory tract infection	7 (10.4)	4 (6.0)	7 (10.6)	18 (9.0)
Investigations, *n* (%)				
Glucose urine present	0 (0.0)	1 (1.5)	1 (1.5)	2 (1.0)
Renal and urinary disorders, *n* (%)				
Proteinuria	1 (1.5)	0 (0.0)	1 (1.5)	2 (1.0)
Skin and subcutaneous tissue disorders, *n* (%)				
Dermatitis atopic	11 (16.4)	6 (9.0)	12 (18.2)	29 (14.5)
Pruritus	5 (7.5)	1 (1.5)	4 (6.1)	10 (5.0)

Treatment-emergent adverse events are categorized according to the Medical Dictionary for Regulatory Activities (MedDRA)/J version 20.0. Data are expressed as number (%).

The mean normalized plasma trough concentrations in the OPA-15406 0.3% and 1% groups were 0.114 ± 0.0991 and 0.113 ± 0.0952 ng/mL per mg, respectively, at week 1, 0.104 ± 0.119 and 0.127 ± 0.119 ng/mL per mg, respectively, at week 4, and 0.0910 ± 0.103 and 0.137 ± 0.242 ng/mL per mg, respectively, at week 8 (Table 4). After multiple twice-daily topical applications, the normalized plasma trough concentrations at weeks 1, 4 and 8 were similar, indicating that no accumulation of OPA-15406 occurred.

Safety assessments

Of the 200 patients included in the study, 78 (39.0%) experienced TEAE. The incidences of TEAE by treatment group were 46.3% (31/67) for the OPA-15406 0.3% group, 29.9% (20/67) for the OPA-15406 1% group and 40.9% (27/66) for the vehicle group. TEAE observed in at least 1% of patients in the total treatment groups are presented in Table 5. The most frequently reported TEAE was worsening of AD, followed by viral upper respiratory tract infection and pruritus. For the OPA-15406 0.3%, OPA-15406 1% and vehicle groups, the incidences of worsening of AD were 16.4% (11/67), 9.0% (6/67) and 18.2% (12/66), respectively; those of viral upper respiratory tract infection were 10.4% (7/67), 6.0% (4/67) and 10.6% (7/66), respectively; and those of pruritus were 7.5% (5/67), 1.5% (1/67) and 6.1% (4/66), respectively.

The incidences of patients who experienced TEAE related to the IMP were 11.9% (8/67) for the OPA-15406 0.3% group, 7.5% (5/67) for the OPA-15406 1% group and 10.6% (7/66) for the vehicle group. Worsening of AD related to the IMP was reported for five patients (7.5%) each in the OPA-15406 0.3% and 1% groups, and for six patients (9.1%) in the vehicle group. Two patients (3.0%) in the OPA-15406 0.3% group experienced IMP-related pruritus. Application site pain and feeling hot, observed in one patient each (1.5% [1/67]) in the OPA-15406 0.3% group, were also judged to be IMP-related TEAE.

The incidences of TEAE leading to discontinuation were 22.4% (15/67) in the OPA-15406 0.3% group, 10.4% (7/67) in the OPA-15406 1% group and 22.7% (15/66) in the vehicle group. The TEAE that most frequently led to discontinuation was worsening of AD (OPA-15406 0.3%, 14.9% [10/67]; OPA-15406 1%, 9.0% [6/67]; vehicle, 18.2% [12/66]), followed by pruritus (OPA-15406 0.3%, 7.5% [5/67]; OPA-15406 1%, 1.5% [1/67]; vehicle, 6.1% [4/66]). No deaths or serious TEAE were reported in this study. All TEAE observed in the OPA-15406 groups were mild or moderate in severity, and there were no severe TEAE. There were no clinically meaningful changes from baseline in clinical laboratory test results, vital sign assessments or 12-lead ECG.

DISCUSSION

The efficacy and safety of OPA-15406 in Japanese patients aged 15–70 years with AD were evaluated in this 8-week, randomized, double-blind, vehicle-controlled study. For the primary end-point, the incidence of success in the IGA score at week 4 was significantly greater in the OPA-15406 1% group relative to the vehicle group. Furthermore, for the secondary end-points, the overall EASI score and subscale scores, the VAS pruritus score and the POEM score were significantly improved and the percentage of affected BSA was significantly decreased as early as week 1 in both OPA-15406 0.3% and 1% groups compared with the vehicle group; the improved scores and decreased percentages were generally maintained until week 8.

Pruritus is the most troublesome symptom of AD to control, defined as an unpleasant sensation that induces a desire to scratch.[8,21] Pruritus in AD patients can lead to sleep disturbance, depression, anxiety, anger, helplessness, reduced self-esteem and difficulty concentrating.[8] Furthermore, the scratching associated with pruritus leads to the signs of AD (e.g. excoriation and lichenification).[22] Based on the patient-reported VAS pruritus score and the investigator-reported excoriation and lichenification scores in the previous[13] and the present phase 2 clinical studies, OPA-15406 demonstrated a significant impact on these typical signs and symptoms of AD.

Topical application of OPA-15406 showed an overall favorable safety profile. No accumulation of topical OPA-15406 from weeks 1 to 8 was noted, based on the normalized plasma trough concentrations. The systemic influence of topical OPA-15406 may be limited considering the PK profiles indicating minimal systemic absorption.

As described above, the present study as well as the previous study[13] demonstrated the favorable efficacy and safety

profiles of topical OPA-15406, indicating a promising treatment option for patients with AD.

This was a phase 2 study with a small sample size for 8 weeks involving adult AD patients. Therefore, further evaluation of OPA-15406 in a large-scale randomized study and long-term (1 year) study including pediatric patients is warranted to ensure the favorable efficacy and safety profiles of OPA-15406 as a therapeutic medication for AD.

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APPENDIX

STUDY INVESTIGATORS

Takashi Onozuka, M.D. (Asanuma Dermatology Clinic, Hokkaido, Japan), Yoshimasa Takahashi, M.D. (Kitago Dept. of Dermatology Clinic, Hokkaido, Japan), Hideyasu Takata, M.D. (Sanrui Dermatology Clinic, Saitama, Japan), Nobuko Yoshihara, M.D. (Yoshihara Dermatology Clinic, Tokyo, Japan), Kazutomo Toyofuku, Ph.D., M.D. (Yamate Dermatological Clinic, Tokyo, Japan), Hiroto Kitahara, M.D. (Kitahara Dermatology Clinic, Tokyo, Japan), Tatsuya Izumi, Ph.D., M.D. (Hiroo Dermatology Clinic, Tokyo, Japan), Toshitatsu Nogita, M.D. (Shinjuku Minamiguchi Hifuka Department of Dermatology, Tokyo, Japan), Aisaku Yamamoto, Ph.D., M.D. (Medical Corporation Kojunkai Kosugi Dermatology Clinic, Kanagawa, Japan), Ichiro Nakasu, M.D. (Nemunoki Dermatology, Kanagawa, Japan), Akihiro Kume, M.D. (Kume Clinic, Osaka, Japan), Akihiro Sasase, Ph.D., M.D. (Sasase Skin Clinic, Osaka, Japan), Masako Watanabe, M.D. (Kobayashi Dermatology Clinic, Hyogo, Japan) and Ken Houki, M.D. (Hohki Dermatology Clinic, Hyogo, Japan).