

ORIGINAL ARTICLE

Effect of topical phosphodiesterase 4 inhibitor E6005 on Japanese children with atopic dermatitis: Results from a randomized, vehicle-controlled exploratory trial

Osamu NEMOTO,¹ Nobukazu HAYASHI,² Yasumi KITAHARA,³ Masutaka FURUE,⁴ Seiichiro HOJO,⁵ Maiko NOMOTO,⁵ Satoshi SHIMA,³ The JAPANESE E6005 Study Investigators*

¹Kojinkai Sapporo Skin Clinic, Hokkaido, ²Department of Dermatology, Toranomon Hospital, ³Japan/Asia Clinical Research, Eisai Co., Ltd., Tokyo, ⁴Department of Dermatology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, ⁵Global Pharmacokinetics & Bioanalysis, Eisai Co., Ltd., Tokyo, Japan

ABSTRACT

This exploratory study was designed to evaluate the safety and efficacy profile of the topical phosphodiesterase 4 inhibitor E6005 in Japanese children with mild-to-moderate atopic dermatitis. The present randomized, multicenter study included 62 patients who were treated with 0.05% E6005, 0.2% E6005 or vehicle ointment twice daily for 2 weeks. Safety and pharmacokinetics were assessed with a focus on the occurrence of adverse events and the whole blood concentrations of E6005 and its metabolite. Exploratory efficacy evaluations included assessments of lesion severity and pruritus score. The 2-week application of topical E6005 was safe and well tolerated with no cutaneous adverse events. The whole blood concentration of E6005 was quantified in only one subject receiving 0.2% E6005 treatment, while its major metabolite was undetectable. The 0.2% E6005 group showed a greater decrease in the severity score than the vehicle group (–45.94% vs –32.26%), although this difference was not statistically significant. Similarly, the treatment success rate according to the investigator's global assessment of the total application sites was higher in the 0.2% E6005 group than in the vehicle group (34.4% vs 20.0%). Moreover, the 0.2% E6005 group showed a greater decrease in the pruritus score than the vehicle group (–37.5% vs –6.7%) in a predefined subpopulation. The efficacy of 0.05% E6005 treatment was comparable to that of vehicle treatment. These results suggest that topical 0.2% E6005 treatment is safe and effective in children with atopic dermatitis, although further large confirmatory clinical trials are warranted.

Key words: atopic dermatitis, children, E6005, phosphodiesterase 4 inhibitor, topical drug.

INTRODUCTION

Atopic dermatitis (AD) is defined as “a disease with repeated exacerbation and remission, chiefly characterized by eczema with itching”.^{1–3} In addition to skin care with moisturizing agents, topical corticosteroids (TCS) are the first-line treatment for adult AD, with an appropriate rank of TCS selected on the basis of the severity of lesions.^{2,3} Topical calcineurin inhibitors (TCI) are indicated in poor responders to TCS or in patients with a high risk of adverse drug reactions.^{4,5} Although treatments for AD in children are basically the same as those in adult patients, milder TCS or lower concentrations of TCI compared with those used in adult patients are selected to prevent the onset of local adverse reactions owing to the generally more sensitive nature of pediatric skin. Therefore, there is a

need for a new treatment option with the long-term use of safer drugs in children with AD.

E6005 is a novel selective inhibitor of phosphodiesterase 4 (PDE4), and use of E6005 may produce topical anti-inflammatory and antipruritic effects and alleviate systemic adverse reactions.^{6–8} In a previous clinical study evaluating the safety and efficacy of treatment with 0.2% E6005 ointment in adult patients with AD, 0.2% E6005 treatment for up to 12 weeks was found to be adequately safe and well tolerated in the patients, and the systemic distribution of E6005 was very limited.⁹ In addition to the favorable safety profile, E6005 treatment for 12 weeks significantly improved efficacy scores from baseline for the affected area/intensity of eczema and pruritus. These findings support the likelihood that topical E6005 may be useful for the long-term management of AD, especially in

Correspondence: Osamu Nemoto, M.D., Kojinkai Sapporo Skin Clinic, H&B Plaza Building 5F, S3W2, Chuo-ku, Sapporo, Hokkaido 060-0063, Japan. Email: osamu.nemoto@gmail.com

*See Appendix for the JAPANESE E6005 Study Investigators.

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pediatric patients. Therefore, an initial study was conducted with the primary objective of evaluating the safety and pharmacokinetics of a 14-day treatment with E6005 ointment (0.05% and 0.2%) in pediatric patients with AD and the secondary objective of providing exploratory assessments of its efficacy.

METHODS

This study was conducted in eight medical institutions in Japan. The study protocol was approved by the institutional review board of each study institution, and the study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All legally responsible representatives (parent or caregiver) of each patient and the patients who were able to understand the decision to participate in the study provided written informed consents for participation before the screening procedures were performed. This study was registered at <http://clinicaltrials.gov> (identifier: NCT02094235). All principal investigators are described in Appendix.

Subjects

The study subjects were enrolled between January and November 2014. Male or female outpatients aged 2–15 years with a definite diagnosis of AD based on the Japanese Dermatological Association's guidelines for the management of AD³ with mild-to-moderate clinical symptoms and at least one evaluable skin lesion at the time of enrollment were eligible for inclusion. Evaluable skin lesions were defined as typical AD skin lesions measuring 25–100 cm² in the trunk or extremities with at least one moderate or severe dermal symptom (erythema, infiltration/papulation, excoriation or lichenification).

The following subjects were excluded: those with a history of biological therapy within 6 months before the study drug application; those who had received systemic therapy such as corticosteroid or immunosuppressant therapy or phototherapy within 28 days before the study drug application; those who had used TCS classified as very strong or strongest³ within 28 days before the study drug application; those who had used weak, medium or strong TCS, or TCI within 7 days before the study drug application, except hydrocortisone butyrate preparations for treatment of areas where the study drug could not be applied, as judged by the investigator (e.g. the skin of the face or head, areas with clinically severe eruptions); and those who had used oral antiallergics indicated for AD treatment in Japan (sodium cromoglycate, oxatomide, supatast tosilate or tranilast) within 14 days before the study drug application. Use of other oral antihistamines and antiallergics was permitted if the same dosing regimens were maintained for at least 14 days before the study drug application. The following subjects were also excluded: those presenting with an active infection and those presenting with Kaposi's varicelliform eruption, scabies, molluscum contagiosum, impetigo contagiosa, psoriasis, Netherton's syndrome or other autoimmune disorders, which may affect the pathological evaluation of AD.

Study design

This was a multicenter, randomized, vehicle-controlled study of the effects of treatment with 0.05% and 0.2% E6005 ointment in children with AD. Pediatric patients with AD were divided into two groups, the older group (school-aged children and adolescents, 7–15 years of age) and the younger group (children, 2–6 years of age), and sequential cohorts of patients from the older and younger groups were treated with 0.05% and 0.2% E6005 ointment (cohorts 1–4), while safety was monitored. Cohort 5 included all pediatric patients from the older and younger groups (Fig. 1).

Subjects who submitted written informed consent and were eligible for inclusion were randomized in a 2:1 allocation to receive treatment with either E6005 ointment (0.05% or 0.2%) or vehicle on day 1 (baseline). According to the lesion size, an appropriate amount of the study drug was applied to all skin lesions, except those on the face or head, twice a day for 14 days (0.5 g of ointment for each area covering two adult palms).¹⁰ Evaluation of the safety, pharmacokinetics and efficacy of the treatments was performed on day 8 (week 1) and day 15 (week 2). A follow-up visit was scheduled 7 days after the last application of the study drug to evaluate the safety and pharmacokinetics of the treatments (day 22).

Assessments

Previous medications used for AD were recorded, and TCS were classified into five categories (strongest, very strong, strong, medium and weak) according to the guidelines for the management of AD.³ Safety assessment included evaluation of the occurrence of adverse events, laboratory test results (hematology, blood chemistry and urinalysis), vital signs, and electrocardiographic and physical findings. Adverse events were assessed according to standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA, version 17.1).

Blood samples were collected on days 8, 15 and 22 in the older group and on day 15 in the younger group by using the dried blood spot method.¹¹ Whole blood concentrations of E6005 and its metabolite M11 (hydrolyzed at the methyl ester bond of E6005) were determined using the validated liquid chromatography-tandem mass spectrometry method (lower

(Planned number)			
Cohort 1	Older group (7 to 15 years)	0.05% E6005 ointment	6
		Vehicle	3
↓ Safety assessments of cohort 1			
Cohort 2	Older group (7 to 15 years)	0.2% E6005 ointment	6
		Vehicle	3
Cohort 3	Younger group (2 to 6 years)	0.05% E6005 ointment	4
		Vehicle	2
↓ Safety assessments of cohort 2 and 3			
Cohort 4	Younger group (2 to 6 years)	0.2% E6005 ointment	4
		Vehicle	2
↓ Safety assessments of cohort 4			
Cohort 5	All (2 to 15 years)	0.2% E6005 ointment	20
		Vehicle	10

Figure 1. Study flow and design.

limit of quantification for both E6005 and M11, 1 ng/mL), by using the same analytical conditions as those used in the plasma assay.¹²

Assessments of skin symptoms were based on the severity scores of the target lesions and the investigator's global assessment (IGA) scores obtained at weeks 1 and 2. Digital photographs of the target lesions, which were determined before the study drug application, were obtained. The intensities of four symptoms (erythema, infiltration/papulation, excoriation and lichenification), which were used in the eczema area and severity index,^{13,14} were evaluated using a 5-point scale (range, 0–4), and the sum of the severity scores of each of the four symptoms represented the total severity score of the target lesions (0–16 points). The severity of the dermal symptoms was also assessed by the IGA of the target lesions (local IGA) and the total application sites (overall IGA) on a 6-point scale (0, clear; 1, almost clear; 2, mild; 3, moderate; 4, severe; 5, very severe).^{15,16} The severity of pruritus was assessed using a 5-point scale (0, clear; 1, almost clear; 2, mild; 3, moderate; 4, severe) at week 2 on the basis of the results of the interviews with the subjects or caregivers. The severity of excoriation of the target lesions was also assessed, and the severity scores were used for the assessment of pruritus.

Statistical analysis

Owing to the exploratory nature of the objectives, no primary end-point was defined in this study, and the sample size was not calculated from a statistical viewpoint. A planned total number of 60 subjects seemed to be sufficient to assess the primary objective of this study.

Subjects who were treated with the study drug at least once and underwent at least one safety or pharmacokinetic assessment were subjected to safety or pharmacokinetic analysis.

Efficacy analyses for the skin symptoms were performed in the full analysis population (i.e. patients in the safety population from whom at least one post-baseline efficacy measurement was available). Assessments of pruritus including the investigator-assessed pruritus scores and severity scores for excoriation of the target lesions were performed in subjects who did not concomitantly use antihistamines or antiallergics during the study. The last observation carried forward (LOCF) imputation method was used to impute missing post-baseline efficacy values.

The primary purpose of inclusion of the 0.05% E6005 treatment was to evaluate the safety of the treatment. Therefore, analyses of the efficacy of the treatment, except the time course of the total severity scores for the target lesions, were performed using data from the vehicle and 0.2% E6005 groups. Student's *t*-test was performed to compare the differences between the 0.2% E6005 and vehicle groups.

RESULTS

Study population, baseline demographics, and clinical characteristics

This study included 62 subjects. Of the 62 subjects randomized, 10 received treatment with 0.05% E6005 ointment, 32

received treatment with 0.2% E6005 ointment and 20 received treatment with vehicle. Sixty-one subjects completed the study, and one subject receiving treatment with vehicle voluntarily discontinued the study (Fig. 2).

Patient demographic characteristics are presented in Table 1. The median age was 7.5 years (range, 2–15), and 33 of the 62 subjects (53.2%) were female. The percentages of the subjects aged 2–6 and 7–15 years were 29.0% (18/62) and 71.0% (44/62), respectively. At baseline, the mean affected area (percent total body surface area) was 17.6 ± 13.6 , and the severity score for the target lesion was 9.9 ± 1.7 . Of the subjects, 82.3% (51/62) and 72.6% (45/62) were classified by local IGA and overall IGA as having moderate disease, respectively. Approximately 90% of the subjects had been treated with a “medium” or “strong” TCS alone or with the concomitant use of these TCS. There were no significant differences in the demographic and clinical characteristics among the groups.

Safety

At both 0.05% and 0.2% concentrations, the E6005 ointment was well tolerated by the subjects. There was no serious or severe treatment-emergent adverse event (TEAE), which was defined as an event occurring at or after the first dose of the study drug until the end of the study. Four (20.0%) subjects in the vehicle group, three (30.0%) subjects in the 0.05% group and one (3.1%) subject in the 0.2% group reported at least one TEAE. None of these TEAEs were classified as a treatment-related TEAE by the investigators. The predefined TEAEs of interest, including application site reaction and skin infection, were not reported. An overview of the TEAEs is presented in Table 2. There were no clinically important changes in clinical laboratory findings, vital signs, or electrocardiographic and physical findings over time.

Pharmacokinetic profiles

Pharmacokinetic analyses showed that topical E6005 was minimally absorbed. The whole blood concentration of E6005 was

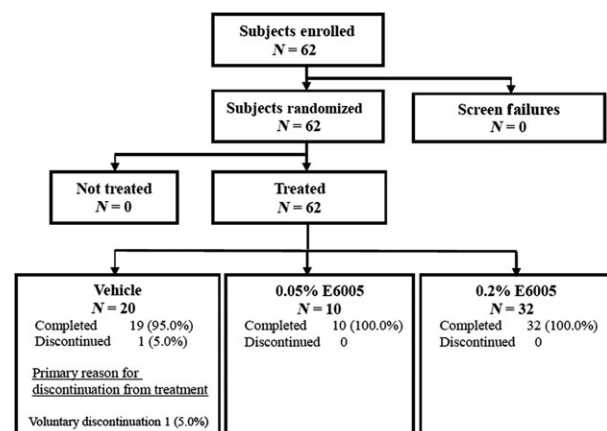


Figure 2. Subject disposition and primary reasons for discontinuation of treatment.

Table 1. Baseline demographics and clinical characteristics

	Vehicle (<i>n</i> = 20)	E6005 0.05% (<i>n</i> = 10)	E6005 0.2% (<i>n</i> = 32)
Demographics			
Age, years, mean (range)	8.3 (2–15)	8.8 (5–15)	8.2 (2–14)
Sex, <i>n</i> (%)			
Male	12 (60.0)	6 (60.0)	11 (34.4)
Female	8 (40.0)	4 (40.0)	21 (65.6)
Weight, kg, mean (range)	32.2 (13.0–75.1)	31.6 (16.8–64.5)	29.0 (11.0–63.0)
Race, <i>n</i> (%)			
Japanese	20 (100.0)	10 (100.0)	32 (100.0)
Clinical characteristics			
Affected area, %TBSA, mean $\pm$ SD	18.5 $\pm$ 12.9	8.9 $\pm$ 5.7	19.9 $\pm$ 15.0
Severity score for target lesions, mean $\pm$ SD	10.3 $\pm$ 2.0	10.1 $\pm$ 1.2	9.7 $\pm$ 1.6
IGA			
Target lesion, mean $\pm$ SD	3.0 $\pm$ 0.6	2.9 $\pm$ 0.3	2.9 $\pm$ 0.4
Total applied site, mean $\pm$ SD	2.8 $\pm$ 0.4	2.5 $\pm$ 0.5	2.8 $\pm$ 0.4
Investigator-assessed pruritus score, mean $\pm$ SD	2.9 $\pm$ 0.5	3.1 $\pm$ 0.3	2.9 $\pm$ 0.4
Prior medications for AD, <i>n</i> (%)			
Oral antiallergics/antihistamines	15 (75.0)	5 (50.0)	24 (75.0)
Topical treatment			
Corticosteroids (all)	18 (90.0)	9 (90.0)	29 (90.6)
Strongest [†]	1 (5.0)	0 (0.0)	2 (6.3)
Very strong [†]	3 (15.0)	1 (10.0)	5 (15.6)
Strong [†]	13 (65.0)	6 (60.0)	17 (53.1)
Medium [†]	18 (90.0)	7 (70.0)	26 (81.3)
Weak [†]	2 (10.0)	1 (10.0)	0 (0.0)
Calcineurin inhibitor	1 (5.0)	1 (10.0)	6 (18.8)

[†]The potency of topical corticosteroids were classified into categories (strongest, very strong, strong, medium and weak) according to the “Guidelines for management of atopic dermatitis”. AD, atopic dermatitis; IGA, investigator’s global assessment; SD, standard deviation; TBSA, total body surface area.

Table 2. Overall incidence of treatment-emergent adverse events (TEAEs)

	Vehicle (<i>n</i> = 20)	E6005 0.05% (<i>n</i> = 10)	E6005 0.2% (<i>n</i> = 32)
All TEAEs [†] , <i>n</i> (%)	4 (20.0)	3 (30.0)	1 (3.1)
Treatment-related TEAEs [‡] , <i>n</i> (%)	0 (0.0)	0 (0.0)	0 (0.0)
TEAEs leading to study discontinuation, <i>n</i> (%)	0 (0.0)	0 (0.0)	0 (0.0)
Serious TEAEs, <i>n</i> (%)	0 (0.0)	0 (0.0)	0 (0.0)
TEAEs–MedDRA [§] preferred term			
Influenza, <i>n</i> (%)	1 (5.0)	1 (10.0)	0 (0.0)
Nasopharyngitis, <i>n</i> (%)	1 (5.0)	2 (20.0)	0 (0.0)
Streptococcal infection, <i>n</i> (%)	0 (0.0)	0 (0.0)	1 (3.1)
Laceration, <i>n</i> (%)	1 (5.0)	0 (0.0)	0 (0.0)
Arthralgia, <i>n</i> (%)	1 (5.0)	0 (0.0)	0 (0.0)

[†]TEAE is defined as an event occurred on or after the first dose of study drug. [‡]Treatment-related TEAEs are TEAEs that are considered by investigators to be possibly or probably related to the study drug or vehicle. [§]MedDRA Version 17.1.

quantified at week 2 in only one sample obtained from a subject receiving 0.2% E6005 treatment (1.65 ng/mL). The whole blood concentrations of M11 were below the lower limit of quantification (<1.00 ng/mL) at all sampling points in all subjects.

Exploratory efficacy

As shown in Figure 3, the total severity scores for the target lesions markedly decreased from week 1 after the study drug application in the 0.2% E6005 and vehicle groups, and the mean percent change in the severity scores was greater in the 0.2% E6005 group than in the vehicle group, although this difference was not statistically significant. Compared to treatment with vehicle, topical treatment with 0.2% E6005 ointment for 2 weeks consistently improved all of the four skin symptoms (erythema, infiltration/papulation, excoriation and lichenification) (Figs S1, S2).

Investigator’s global assessment showed greater improvements in the target lesions and the total application sites in the 0.2% E6005 group than in the vehicle group. According to local IGA and overall IGA, the treatment success rate, defined as the percentage of subjects achieving a “clear” (score 0) or “almost clear” (score 1), was 40.6% (13/32) or 34.4% (11/32) at week 2/LOCF in the 0.2% E6005 group, whereas it was 25.0% (5/20) or 20.0% (4/20) in the vehicle group. Skin symptoms according to the severity scores in the 0.05% E6005 group decreased over time, but this change was almost similar to that in the vehicle group (Fig. 3).

The effects of treatments on itching were analyzed in subjects who did not concomitantly use antihistamines or antiallergics during the study. As shown in Figure 4, the severity

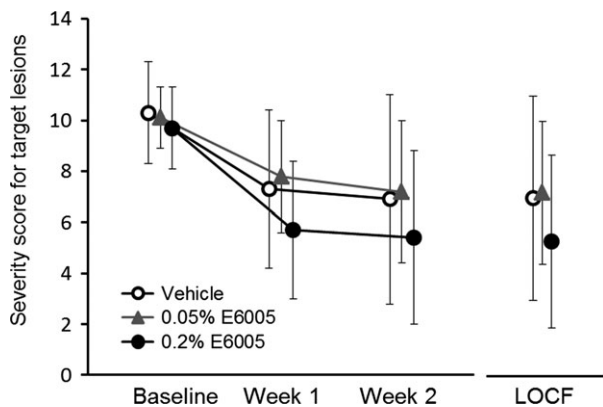


Figure 3. Clinical responses to the E6005 and vehicle treatments over time. Values are presented as mean $\pm$ standard deviation. Vehicle, $n = 20$ (at baseline and last observation carried forward [LOCF]) or $n = 19$ (at weeks 1 and 2); 0.05% E6005, $n = 10$; 0.2% E6005, $n = 32$ (at baseline, week 1 and LOCF) or $n = 31$ (at week 2).

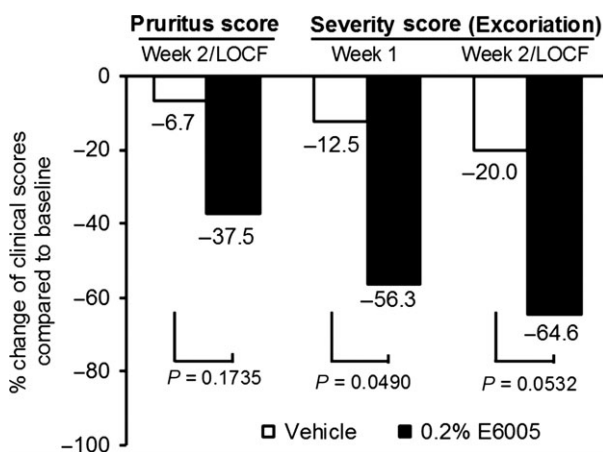


Figure 4. Effects of the treatments on itching in subjects who did not use antihistamines or antiallergics. The mean values of the percentage changes in the investigator-assessed pruritus scores (left) from baseline to week 2/last observation carried forward (LOCF) and severity scores for excoriation of the target lesions (right) from baseline to week 1 and week 2/LOCF are shown. Vehicle, $n = 4$ at week 1 and $n = 5$ at week 2/LOCF; 0.2% E6005, $n = 8$ at both time points. Student's t -test was performed to compare the differences between the 0.2% E6005 and vehicle groups.

scores for excoriation of the target lesions showed a greater statistically significant decrease at week 1 in the 0.2% E6005 group than in the vehicle group (-56.3% vs -12.5% , $P = 0.0490$). Moreover, the investigator-assessed pruritus scores and severity scores for excoriation showed a greater decrease at week 2/LOCF in the 0.2% E6005 group than in the vehicle group, but this difference was not statistically significant.

DISCUSSION

To our knowledge, this multicenter, randomized, vehicle-controlled study is the first to primarily evaluate the safety and pharmacokinetics of treatment with E6005, a new topical PDE4 inhibitor, in pediatric patients with AD. Our findings demonstrate that treatment with 0.05% or 0.2% E6005 ointment was adequately safe and well tolerated in pediatric patients with AD, and there were no clinically important changes in clinical laboratory findings, vital signs or electrocardiographic findings. Furthermore, there were no cases of skin infections or adverse reactions, including burning sensations and skin atrophy, at the application sites. Our results showing the favorable safety profile of treatment with topical E6005 are consistent with those of a previous study that evaluated the safety and efficacy of treatment with 0.2% E6005 ointment in adult patients with AD.⁹ Several clinical trials have demonstrated that the application of topical tacrolimus, an effective treatment option for pediatric AD worldwide, induces transient but relatively frequent burning sensations at the application sites.^{4,17–20} In terms of the systemic and application site side-effects, E6005 treatment may be a better and safer alternative to the existing topical treatments for AD. Regarding the pharmacokinetic profile, the whole blood concentration of E6005 was quantified at week 2 in only one sample from one subject in the 0.2% E6005 group, while the E6005 level was 1.65 ng/mL, which was slightly above the lower limit of quantification (1.00 ng/mL). The whole blood concentrations of M11 were below the lower limit of quantification at all samples in all subjects. These results suggest that most of the applied E6005 did not enter the systemic circulation in the pediatric subjects. In a previous study including adult subjects with AD, only plasma concentrations of M11, not E6005, were quantified (up to 13.6 ng/mL) by a 12-week application of 0.2% E6005 ointment.⁹ Because blood-to-plasma ratios of E6005 and M11 were similar, at 0.690 and 0.594 at 3 ng/mL, respectively (T. Ishii, unpubl. data), differences in the analytical matrix (plasma in adult patients and blood in pediatric patients) were not responsible for the differences in the E6005 and M11 concentrations between the adult and pediatric patients. The metabolism of E6005 is mediated by carboxylesterase, which is known to show large inter-individual variability and age-dependent expression.²¹ This may be one of the possible reasons for the differences in the E6005 concentrations between the adult and pediatric patients. A potential weakness or limitation of this study is that the study drug was not applied to the skin of the face and head in pediatric patients because this study was the first clinical trial of E6005 in pediatric patients and was therefore controlled to avoid any drastic exposure to E6005 and M11.

The secondary objective of this study was to assess the exploratory efficacy profile of topical E6005 in pediatric patients with AD. Compared with the severity scores in the vehicle group, those in the 0.2% E6005 group, especially the subscores for erythema, excoriation and lichenification of the target lesions, showed improvement within the first week. In addition, IGA showed that the treatment success rate (achievement of “clear” or “almost clear”) at week 2 in the 0.2% E6005 group was 40.6% for targeted eczema (vehicle,

25.0%) and 34.4% for the total application sites (vehicle, 20.0%). Although data should be interpreted with caution considering the different study designs, study durations and sample sizes, the treatment success rate in the present study was considered to be comparable with that in a pooled analysis of two phase III studies of topical pimecrolimus (1% cream), a non-steroidal calcineurin inhibitor approved for the treatment of pediatric AD with mild-to-moderate severity.¹⁵ On the other hand, the fact that 0.05% E6005 treatment did not show greater efficacy than vehicle treatment indicates that the effective concentration of E6005 may be 0.2% or more. Regarding antipruritic effects in subjects who did not concomitantly use antihistamines or antiallergics during the study, the investigator-assessed pruritus scores were greatly improved with the 0.2% E6005 treatment. Another important finding is that compared with the vehicle group, the 0.2% E6005 group showed a significant improvement in excoriation, which is consistent with the improvement in the pruritus score. Several antipruritic mechanisms of topical E6005 have been proposed recently: (i) direct inhibition of the PDE4B subtype expressed in dorsal root ganglion neurons; (ii) suppression of the upregulation of skin nerve growth factor levels; and (iii) inhibition of responses to proteinase-activated receptor 2 stimulation.^{7,8,22,23}

The limitations of this exploratory study include its small sample size, which was not calculated from a statistical viewpoint, the concomitant use of antiallergics, the restricted availability of application sites (the skin of the face and head was not an application site), and the short study period (2 weeks), which might not have allowed adequate assessment of the clinical efficacy of treatment with topical E6005 for chronic AD. Therefore, further trials with larger sample sizes and longer study periods are warranted to confirm our findings. In addition to the above, this study was in an investigator-blinded manner because the colors of E6005 ointments and vehicle are slightly different. In order to reduce evaluation bias, the study was conducted in a manner similar to that in a double-blind study by: (i) placing the study drugs in unidentifiable tubes and packing the tubes in unidentifiable containers; and (ii) not informing subjects or investigators about the color of the study drugs.

In conclusion, the present study showed that topical treatment with 0.2% E6005 ointment for 14 days was well tolerated, with very low systemic exposure, in pediatric patients with AD. The exploratory evaluations demonstrated the favorable efficacy of this treatment, which is expected to be comparable with the efficacy of treatment with mild TCI. Therefore, topical E6005 is one possible option as safe and effective treatment in pediatric patients with AD.

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APPENDIX

THE JAPANESE E6005 STUDY INVESTIGATORS

Hiroyuki Asanuma (Asanuma Dermatology Clinic), Kenji Saga (Ario-Sapporo Dermatology Clinic), Yoshimasa Takahashi

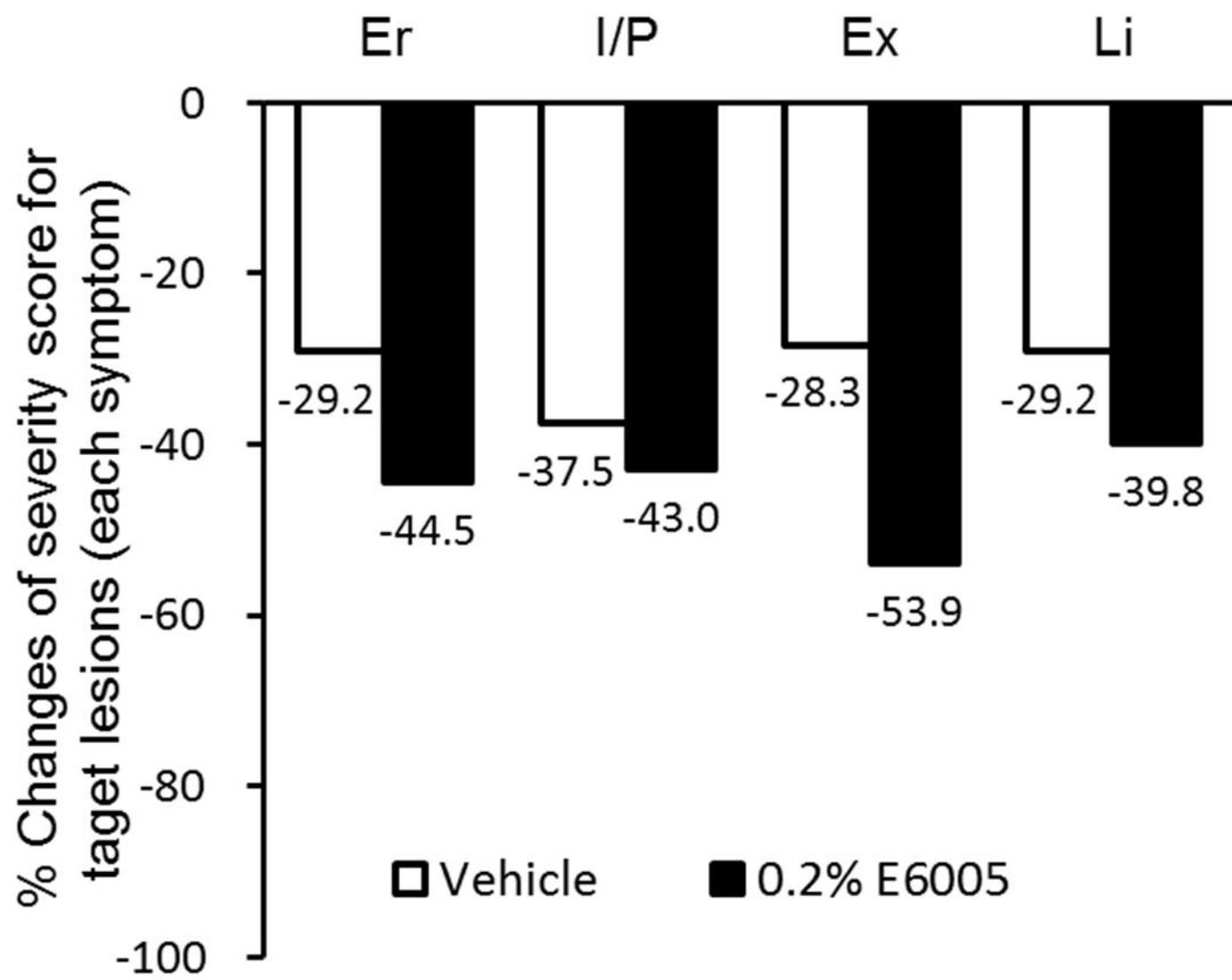
(Kitago Dermatology Clinic), Reiko Morikawa (Megumino Dermatology Clinic), Kazuya Hagiwara (Yamahana Dermatology Clinic), Hiroshi Sugawara (Kokubu Dermatological Clinic), Hideyasu Takata (Sanrui Dermatology Clinic), and Takafumi Etoh (Tokyo Teishin Hospital).

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1. The effect on intensity of each symptom on the target lesions at week 2/last observation carried forward (LOCF). Shown are mean values of percent change from baseline of severity scores for the symptoms of erythema (Er), induration/papulation (I/P), excoriation (Ex) and lichenification (Li) in the vehicle group ($n = 20$) and the 0.2% E6005 group ($n = 32$).

Figure S2. Clinical photographs of two subjects treated with 0.2% E6005 ointment showing symptomatic improvement. In one subject, the total severity score of targeted lesion decreased from (a) score 10 at baseline to (b) score 2 at week 2 with improvement in the symptom of erythema and excoriation. In another subject, the score decreased from (c) score 11 at baseline to (d) score 4 at week 2 with improvement of induration/papulation and excoriation.



(a)



(b)



(c)



(d)

