



# Efficacy of Pseudo-Ceramide-Containing Steroid Lamellar Cream in Patients with Mild to Moderate Atopic Dermatitis: A Randomized, Double-Blind Study

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Received: March 10, 2022 / Accepted: June 23, 2022 / Published online: July 19, 2022  
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## ABSTRACT

**Introduction:** Atopic dermatitis (AD) is a chronic inflammatory skin disorder involving decreased barrier function of the stratum corneum. This decrease, caused by a reduction in ceramide, the primary component of intercellular lipids in the stratum corneum, leads to a disturbance in the lamellar structure.

**Methods:** We developed a formulation (test cream) containing a steroid and synthetic pseudo-ceramide (SLE: *N*-(3-hexadecyloxy-2-hydroxypropyl)-*N*-2-hydroxyethyl hexadecanamide) that forms a lamellar structure on the skin after its application and drying. The formulation or control cream (a formulation

containing a steroid but not pseudo-ceramide that does not form a lamellar structure) was applied twice daily for 2 weeks to the lesional area of 34 participants with mild to moderate AD symptoms.

**Results:** The test cream showed a periodic structure with an interface space of approximately 8.2 nm in transmission electron microscopy and small- and wide-angle X-ray scattering, similar to the lamellar structure in the human stratum corneum. In the double-blind test, the anti-inflammatory effects of the test cream ( $n = 17$ ) were comparable to those of the control cream ( $n = 17$ ). In the test cream group, a significant increase in the stratum corneum moisture content ( $p < 0.01$ ) and significant decrease in transepidermal water loss ( $p < 0.05$ ) were observed at weeks 1 and 2 after application compared with those before application. No such change was observed in the control group.

**Conclusion:** The results indicate that, even with a relatively short application period of 2 weeks, the test cream not only suppressed inflammation of the lesional area, but also improved the inherent barrier function of the stratum corneum, suggesting its potential as a treatment option for patients with AD.

**Keywords:** Atopic dermatitis; Comparative study; Steroid; Lamella; Pseudo-ceramide

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## Key Summary Points

### *Why carry out this study?*

Atopic dermatitis (AD) is an inflammatory skin disorder that presents with decreased barrier function in the stratum corneum.

A decrease in the amount of intercellular lipids, the main component of which is ceramide, and changes in their structure contribute to the decreased barrier function of the stratum corneum in AD.

We aimed to evaluate the efficacy of a cream containing a steroid and pseudo-ceramide that forms a lamellar structure in patients with AD.

### *What was learned from the study?*

The test cream exhibited anti-inflammatory effects and improved the barrier function of the stratum corneum in the AD lesional area within a short period.

The test cream containing pseudo-ceramide with a lamellar structure can be used as a treatment option for patients with AD.

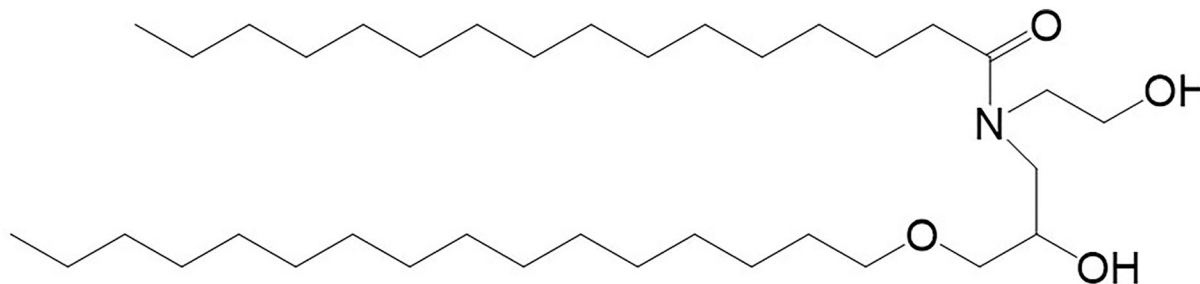
## INTRODUCTION

Atopic dermatitis (AD) is an inflammatory skin disorder that presents with decreased barrier function in the stratum corneum, enabling irritants and allergens to easily infiltrate the skin and induce inflammatory and allergic responses. Therefore, skincare regimens that enhance barrier function in addition to treatment with drugs such as anti-inflammatory agents and anti-allergy medications are used [1, 2]. Typically, skincare consists of using moisturizing agents such as heparinoid, which reduce skin irritation and improve epidermal cell turnover, thereby improving the barrier function of the stratum corneum [3–5].

However, this effect is indirect and not immediate. Decreased barrier function of the stratum corneum is also observed in nonlesional areas; however, the decrease is considerably greater in lesional areas, where an inflammatory response is likely to recur with the infiltration of irritants, even with drug-induced suppression of inflammation [6]. In addition, *Staphylococcus aureus* releases aggravating factors in AD [7]. Therefore, it is desirable to immediately enhance the inherent barrier function of the skin at lesional sites, which exhibit poor stratum corneum functions (i.e., moisture and barrier) and are prone to inflammation recurrence.

The barrier function of the stratum corneum is attributed to the presence of intercellular lipids [8] derived from extracellular release of lamellar granules from epidermal cells [9]. In AD, the size of lamellar granules and number of released lamellar granules decrease [10]. In addition, the level of ceramides, the primary components of these intercellular lipids, is diminished in AD. Furthermore, the composition of fatty acids and ceramides is altered [11, 12], resulting in an abnormal intercellular lipid structure in the stratum corneum of individuals with AD [13, 14]. A decrease in the amount of intercellular lipids and changes in their structure are thought to contribute to the decreased barrier function of the stratum corneum in AD.

AD symptoms improve following supplementation of synthesized pseudo-ceramide (SLE: *N*-(3-hexadecyloxy-2-hydroxypropyl)-*N*-2-hydroxyethyl hexadecanamide (Fig. 1)) or ceramides [15–25]. We hypothesized that improving the barrier function of the stratum corneum by supplementation of SLE and delivering agents that form a lamellar structure similar to that of the intercellular lipids would improve AD. An SLE-containing steroid formulation that forms a lamellar structure on the skin surface after application and drying may be useful for suppressing inflammation in the lesional area and improving the barrier function of the stratum corneum in patients with AD. Therefore, we developed a steroid formulation and evaluated its usefulness in ameliorating the barrier function of the stratum corneum in the lesional areas of patients with AD.



**Fig. 1** Structure of synthetic pseudo-ceramide (SLE: *N*-(3-hexadecyloxy-2-hydroxypropyl)-*N*-2-hydroxyethyl hexadecanamide)

## METHODS

### Test Cream

The test cream was an oil-in-water cream formulation containing 0.15% prednisolone valerate acetate (PVA) and 3% synthetic pseudo-ceramide. The other components were cetyl alcohol, stearyl alcohol, polyoxyethylene sorbitan monostearate, sorbitan monostearate, glycerin, and water. The control cream was an oil-in-water-type commercial steroid cream containing 0.15% PVA, based on Vaseline, with cetyl alcohol, stearyl alcohol, polyoxyethylene sorbitan monostearate, and sorbitan monostearate.

### Structural Analysis of the Formulation Film

#### *Specimen Preparation for Transmission Electron Microscopy*

The structures of the dried films of the test and control creams were observed as follows. Briefly, each cream was applied with a coater (thickness of 120  $\mu\text{m}$ ) on a polyethylene terephthalate overhead projector film. After 3 h of drying, 5-mm squares were cut out, stained, and fixed with osmium tetroxide for 24 h at room temperature (23  $^{\circ}\text{C}$ ). A Leica UC-6 cryo-ultramicrotome (Leica Microsystems, Wetzlar, Germany) was used to obtain ultrathin sections of 50–100-nm thickness at  $-80^{\circ}\text{C}$ . The sections were collected in droplets of frozen 2.3-M sucrose, placed on a grid (200 mesh with support film, without carbon reinforcement), washed, and

dried. H-7650 (Hitachi, Tokyo, Japan) was used to perform measurements at an acceleration voltage of 80–100 kV. A charge-coupled device (1024  $\times$  1024 pixels) was used for detection.

#### *Small- and Wide-Angle X-Ray Scattering*

The dried films of the test and control creams were evaluated using a small- and wide-angle X-ray scattering apparatus (SAXSess mc<sup>2</sup>; Anton Paar GmbH, Graz, Austria). For sampling of the dried film, the substance was applied on a polyethylene terephthalate resin overhead projector film with a coater (120  $\mu\text{m}$  thickness), dried for 3 h, scraped with a spatula, and placed into cells. Paste cells specific for SAXSess mc<sup>2</sup> were used as sample cells. X-Ray scatter detection was performed using an imaging plate for SAXSess mc<sup>2</sup>. The measurement conditions were as follows: X-ray wavelength, 0.1542 nm; sample–detector distance, 259.2 mm; and measurement temperature, 25  $^{\circ}\text{C}$ . The exposure time was set at 5–60 min on the basis of the balance between the irradiation limit of the Imagine Plate and detection sensitivity (signal-to-noise ratio). After exposure to the imaging plate, on the basis of the acquired two-dimensional scattering images, a one-dimensional scattering profile was created using the accessory software provided with SAXSess mc<sup>2</sup> (SAXSquant 2D; SAXSquant, Anton Paar GmbH). The period  $d$  [nm] of the lamellar structure observed on X-ray scattering was determined from the peak position as follows:  $q = 2\pi/d$  [ $\text{nm}^{-1}$ ], where  $q$  is the scattering vector.

## Efficacy Test

### **Subjects**

A parallel, randomized, double-blind, dermatologist-controlled baseline comparison study was performed from May to November 2016 in Hokkaido, Japan (UMIN registration no. 000022212). The study adhered to the tenets of the Declaration of Helsinki, and all clinical studies were reviewed and approved by the Review Board of Kao Corporation (Tokyo, Japan) and Medical Corporation Kojinkai Sapporo Skin Clinic (Sapporo, Japan). Written informed consent was obtained from each subject prior to the study.

Subjects with mild to moderate skin symptoms of AD on the inner forearm were prescreened from candidates by visual observation and medical interviews conducted by dermatologists. Subjects who received medical treatment on their face were excluded. Among the 59 Japanese patients who were prescreened, 36 subjects aged 16–49 years (mean,  $28.9 \pm 0.9$  years) were enrolled in this study.

Among the patients with AD (age range, 16–49 years) presenting with mild to moderate grade at the test site (inside of the left forearm), who fully understood the significance, content, and purpose of the study and wished to participate in this study, 36 were selected as eligible candidates by the investigator and study director.

### **Evaluation Flow**

After screening, the 36 selected participants were divided into the test formulation application group ( $n = 18$ ) and control cream application group ( $n = 18$ ) on the basis of age, sex, and dermatologist evaluation indices.

After a 1-week washout period (–1 W), the application of the test formulation was started, and the participant was interviewed by a dermatologist. The test site was visually evaluated, measured, and photographed at the start of test formulation application (W0), 1 week (W1), and 2 weeks (W2). Severity assessment using photographs was conducted after the application period (Fig. 2).

During the washout period, the subjects were requested to abstain from applying any formulations such as moisturizing agents or medications to the test site and to refrain from taking other medications for AD. However, if the skin condition worsened markedly during this period, the subject was excluded from the study, and the patient received appropriate treatment from a dermatologist.

### **Application of Test or Control Cream**

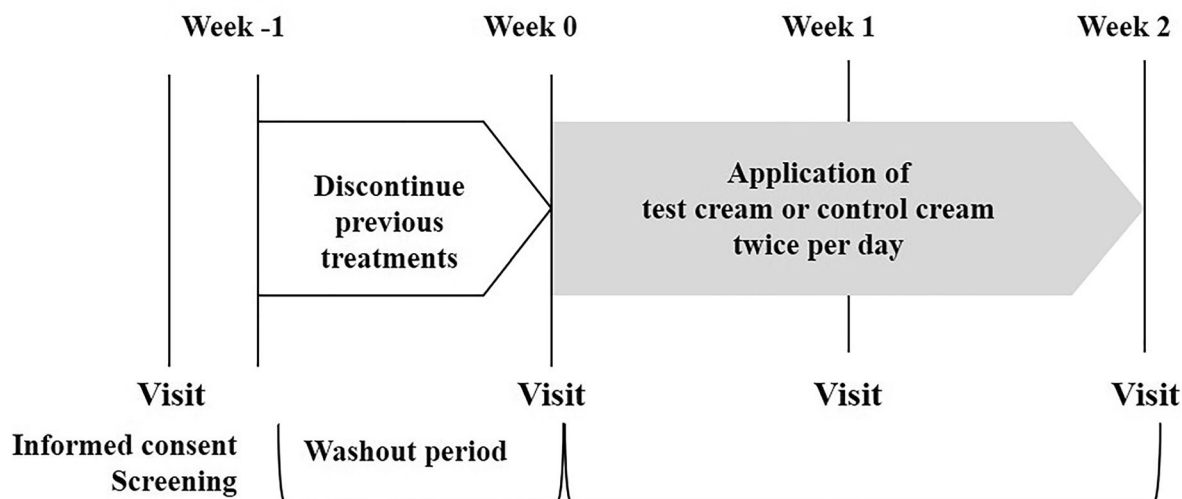
Test cream (approximately 0.5 g) or control cream was applied to the forearm twice daily, once in the morning and once at night, for 2 weeks. The participants were allowed to apply the drug to non-test sites. When abnormalities were observed in the application site during the study, the dermatologist provided appropriate treatment, and drug use was discontinued as necessary. Application of other moisturizing agents or topical agents to the test site during the usage period was prohibited. Switching of cleansing agents was not allowed. The application of skincare products at non-test sites was allowed.

### **Evaluation and Measurement**

After washing the test site with water and thoroughly wiping off the moisture, the subjects were acclimatized at  $20 \pm 2$  °C and  $45.0 \pm 5.0\%$  humidity for at least 20 min before evaluation and measurement. The same location was measured every time by making a transparent sheet showing the measurement site for each subject. The sheet was applied on their arms, and the measurement site was marked before acclimatization.

### **Interview, Examination, and Severity Assessment**

Interviews and examinations were performed at W0, W1, and W2 visits. The test sites were photographed with a Canon EOS Kiss X5 camera (lens: EF-S60mm f/2.8 Macro USM, Canon, Tokyo, Japan). Severity assessment of the test sites was performed using the photographs taken at W0, W1, and W2 after W2 examination. A dermatologist assigned severity scores of 1–4 (1, mild; 2, moderate; 3, severe; 4, very



**Fig. 2** Test design. Following the 1-week washout period, test cream or control cream was applied twice per day on the arm for 2 weeks

severe) based on the severity classification (simple method) of AD, which is comprehensively determined by the degree and areas of eruption considering these eight factors: erythema, papules, erosion, crusts, excoriation, lichenification, pruriginous nodules, and depilation. It was developed by the advisory committee of the AD severity classification of the Japanese Dermatological Association [26].

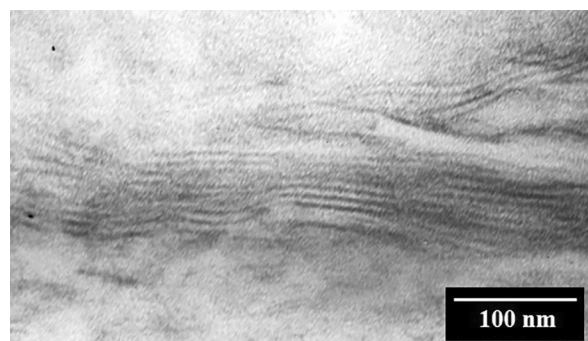
### **Skin Property Measurement**

The moisture content in the stratum corneum at each test site was measured using SKICON-200EX (IBS, Hamamatsu, Japan). The test site was measured at five points, and the mean from the middle three values (after excluding the highest and lowest values) was defined as the measurement value. Transepidermal water loss (TEWL) was measured at one point in the test site on the left arm using Tewameter TM300 (Courage + Khazaka electronic GmbH, Köln, Germany).

### **Statistics**

Significance analysis was performed after determining the target participants for effectiveness evaluation based on a usage rate (%) of at least 80% of the test formulation and

compliance status. For significance testing, the results of photographic severity assessment were analyzed using Mann–Whitney *U* test between groups and Scheffé’s multiple comparison test within groups. Skin property measurement values were calculated as the changes from the start date (W0). The results were analyzed using Student’s *t*-test between groups and the Holm–Bonferroni method for within-group comparisons. Statistical significance was set at a 95% confidence interval ( $P < 0.05$ ). Statistical analyses were performed using SPSS Statistics software (version 19; SPSS, Inc., Chicago, IL,



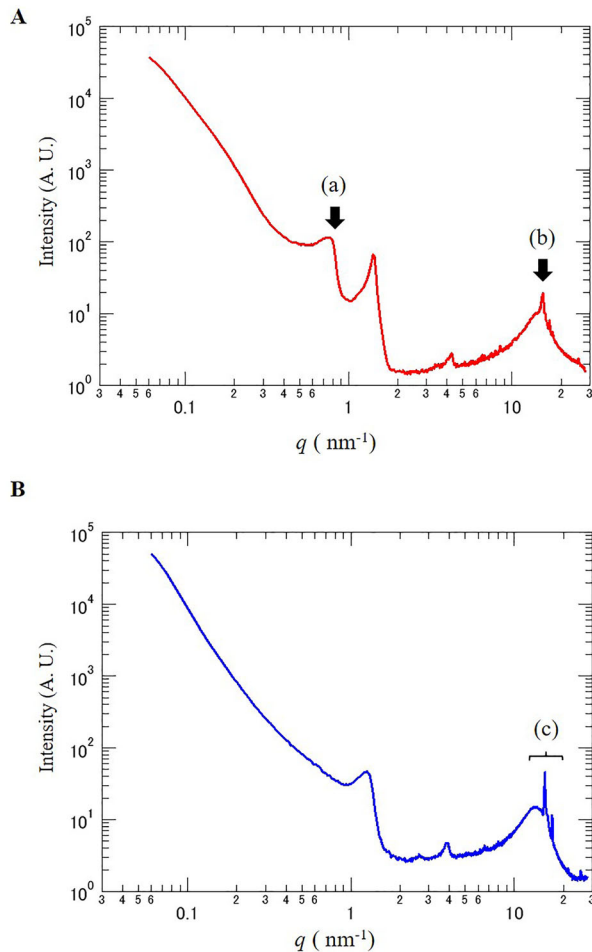
**Fig. 3** Lamellar structure of the test cream under a transmission electron microscope. The layered structure with intervals of less than 10 nm was observed

USA) and Ekuseru-Toukei 2012 (Social Survey Research Information Co., Ltd, Tokyo, Japan).

## RESULTS

### Structural Analysis of Film Formulation

The lamellar structure of the test cream was confirmed using transmission electron microscopy. A layered structure with intervals of less



**Fig. 4** Structure of the test and control cream analyzed using X-ray scattering analysis. **A** The test cream (red line) showed a peak at  $q = 0.765$  nm<sup>-1</sup> and a lamellar structure with a periodicity phase of approximately 8.2 nm (a). A clear peak was also observed at  $q = 15.4$  nm<sup>-1</sup> in the test cream (b). **B** The control cream (blue line) showed no clear peak within the  $q = 0.05$ – $1$  nm<sup>-1</sup> range. Multiple peaks from crystal structures appeared around  $q = 15.4$  nm<sup>-1</sup> in the control cream (c)

than 10 nm was observed (Fig. 3). However, no such lamellar structure was observed for the control cream (data not shown). The X-ray analysis was performed to confirm the detailed lamellar structure. The X-ray one-dimensional scattering profile of the dried test cream on the film showed a peak at  $q = 0.765$  nm<sup>-1</sup> [Fig. 4A (a)]. The periodicity phase of the test cream was approximately 8.2 nm, and a lamellar structure was formed after application and drying. No clear peak was observed within the  $q = 0.05$ – $1$  nm<sup>-1</sup> range for the control cream (Fig. 4B), whereas a clear peak was observed at  $q = 15.4$  nm<sup>-1</sup> for the test cream [Fig. 4A (b)], although multiple peaks appeared in this position for the control cream [Fig. 4B (c)]. This result indicates that the test cream had an  $\alpha$ -gel structure, and some intercellular lipids in the human stratum corneum have been shown to have the same structure. These results demonstrate that a lamellar structure was formed after applying the test cream.

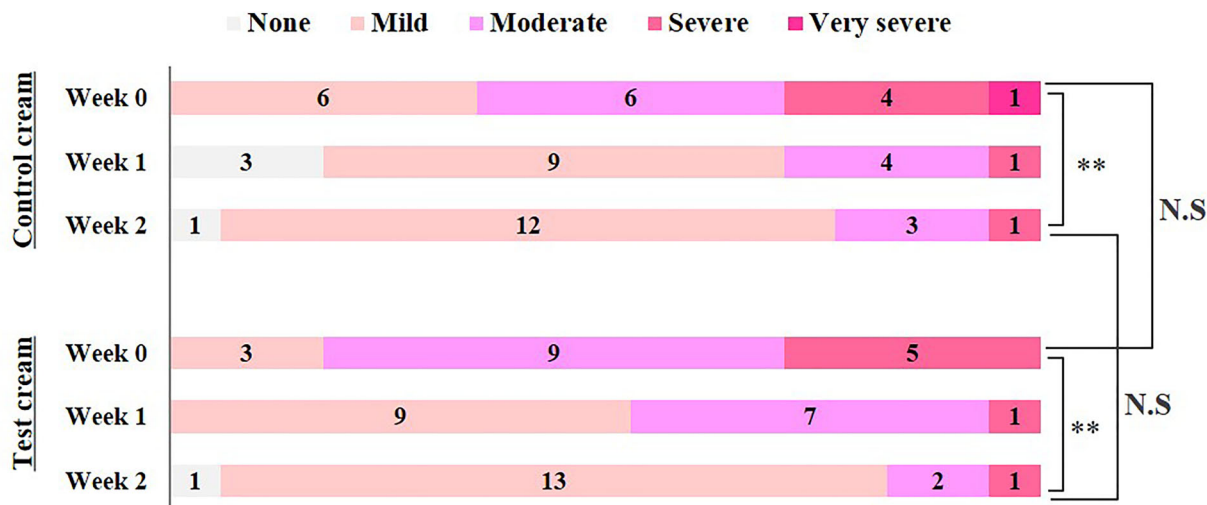
### Efficacy Test

During the 1-week washout period before application, none of the participants exhibited progression in the condition that required treatment, and all 36 participants applied the formulation for 2 weeks. However, a subject in the control cream group could not appear at W2 visit and a subject in the test cream group did not apply the cream twice per day. Therefore, these subjects were excluded, and the efficacy in and skin properties of the remaining control cream group ( $n = 17$ ) and test cream group ( $n = 17$ ) subjects were evaluated.

### Safety and Efficacy

Interview and examination by a dermatologist did not reveal drug-related adverse effects of either the test cream or control cream, suggesting comparable effectiveness and safety between the creams.

The photographic severity assessment showed that 2 weeks of application significantly improved symptoms compared with those before application in both test and control



**Fig. 5** Assessment of severity at the test sites following drug application. Significant improvements were observed between weeks 0 and 2 in both groups. No significant differences were observed between the groups ( $p < 0.01$  for both). However, no significant difference in the degree of improvement was evident between the groups (Fig. 5).

differences were observed between the groups.  $*p < 0.01$  (Scheffé’s multiple comparison test)

### Measurement of Skin Properties

The moisture content in the stratum corneum in the test and control cream groups is shown in Fig. 6A. In the test cream group, the changes in the skin hydration value compared with that at W0 were  $48.0 \pm 13.0$  at W1 and  $44.7 \pm 11.2$  at W2, indicating significant increases [mean  $\pm$  standard error (SE),  $p < 0.01$  at both W1 and W2]. In contrast, the values of the control cream group were  $-3.4 \pm 3.6$  at W1 and  $3.8 \pm 5.5$  at W2, indicating no significant changes. The changes in skin hydration values at weeks 1 and 2 in the test cream group were significantly higher than those in the control cream group ( $p < 0.01$ ).

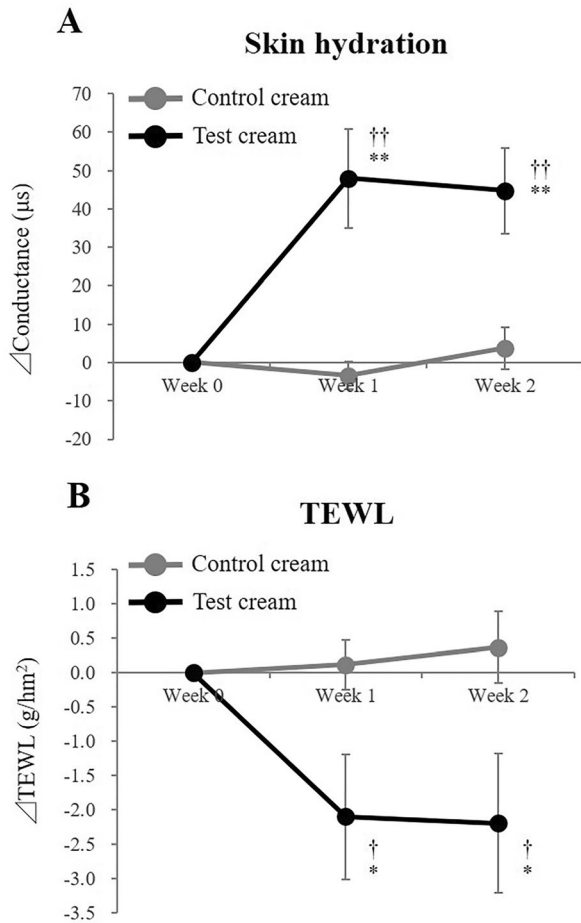
The TEWL values of the test and control cream groups are shown in Fig. 6B. The changes in TEWL from that at W0 in the test cream group were  $-2.1 \pm 0.9$  and  $-2.2 \pm 1.0$  g/hm<sup>2</sup> at W1 and W2, respectively, showing a significant decrease compared with that before application (mean  $\pm$  SE,  $p < 0.05$  at both W1 and W2). In contrast, the values of the control cream group were  $0.1 \pm 0.4$  and  $0.4 \pm 0.5$  g/hm<sup>2</sup> at W1 and W2, respectively, indicating no significant

changes. The changes in TEWL in the test cream group at weeks 1 and 2 were significantly lower than those in the control group ( $p < 0.05$ ).

### DISCUSSION

On the basis of the efficacy test, the formulation that formed a lamellar structure on the skin after drying displayed effects comparable to those obtained with the formulation that did not form such a structure, improving AD eczema (Fig. 5). This was likely because we included patients who presented with relatively mild AD symptoms (mild to moderate grade). Therefore, although PVA (a relatively weak steroid) was used, both treatments resulted in apparent improvements [27]. We also evaluated permeability in an infinite capacity system using porcine skin and verified that the test and control creams showed permeability comparable to that of PVA at 24 h after application (data not shown). These results indicate that the test cream was as effective and safe as the control cream.

The severity assessment revealed comparable improvements; however, skin hydration significantly increased and the TEWL significantly decreased with the test cream compared with the control cream (Fig. 6). These results indicate



**Fig. 6** Changes in skin hydration and transepidermal water loss. **A** No significant changes in the control group ( $n = 17$ ). Significant increase in the test cream group ( $n = 17$ ) (mean  $\pm$  SE,  $**p < 0.01$ , Holm–Bonferroni method, versus week 0). The changes in the skin hydration value at weeks 1 and 2 in the test cream group were significantly higher than those in the control cream group ( $^{\dagger\dagger}p < 0.01$ , Student’s  $t$ -test). **B** Transepidermal water loss significantly decreased in the test cream group following application (mean  $\pm$  SE,  $*p < 0.05$ , Holm–Bonferroni method, versus week 0). The changes in transepidermal water loss in the test cream group at weeks 1 and 2 were significantly lower than those in the control cream group ( $^{\dagger}p < 0.05$ , Student’s  $t$ -test)

that the test formulation possessing a lamellar structure improves the stratum corneum function.

In general, to stably emulsify a steroid with high crystallinity, dissolution in polar oils is essential. However, polar oils can easily destroy the lamellar structure of the formulation.

Therefore, preparing a steroid formulation that maintains the lamellar structure after drying is extremely challenging. However, we identified a stable emulsification region and developed this formulation by combining a steroid and SLE with multiple higher alcohols and surfactants with different critical packing parameters [28, 29].

In this study, we confirmed that the periodicity phase of the lamellar layer formed on the skin after applying and drying the test cream was approximately 8.2 nm (Figs. 3, 4). The periodic structure of lamella was observed in the human stratum corneum, and the structure is important to maintaining barrier and moisturizing function [30–32]. It was confirmed that this formulation also had a lamella structure, although the distance of the lamellar phases was slightly different. However, by having a lamella structure, the test cream should contribute to improve barrier and moisturizing function.

After application and drying the test cream, a lamellar structure coated the skin. This not only led to anti-inflammatory effects, but also increased the barrier and moisturizing functions, normalizing epidermal turnover more rapidly. This may explain the improvements in stratum corneum function. When covering the skin, a complete seal would result in maceration, the tissue destruction from long-term exposure to high humidity, of the healthy surrounding tissue, delaying barrier healing. Therefore, an appropriate moisture permeability is necessary [33–36]. The lamellar structure formed by the test cream after application and drying, unlike that observed with plastic wrap that completely seals objects, exhibits adequate moisture permeability, thus functioning as a physical protective film on the skin. Following disruption of the skin barrier with acetone ether, a formulation with a lamellar structure promotes barrier recovery [28]. Therefore, the test cream, even after a relatively short application period of 2 weeks, promoted and normalized ceramide production and turnover within the skin at the lesional area by ensuring appropriate occlusion and improved the barrier function of the stratum corneum in participants.



The skin of patients with AD shows a markedly decreased stratum corneum barrier function in both lesional and nonlesional areas compared with the skin of healthy individuals [6]. Thus, even after the management of dermatitis with steroid treatment, the abnormal barrier function in the nonlesional area does not normalize. The test cream improved the inherent barrier function of the skin through its anti-inflammatory effects as a drug, as well as by its high-moisturizing function as a skincare product. Proactive therapy for AD requires thorough suppression of inflammation by applying steroids to the non-lesional area and improving the function of the stratum corneum [37]. For this reason, the cream contained anti-inflammation agents and pseudo-ceramide with a lamellar structure may be useful for proactive therapy, but since the side effects of long-term use of steroids are also of concern, it is necessary to consider the period of use when using steroids as anti-inflammatory agents.

In addition, it is possible to reduce the steroid dose or use a weaker class (potency) of steroids. The compliance rate with topical agents is lower in patients with AD than in patients with other dermatitis conditions [38, 39]. The test cream does not require the use of other topical agents or skincare agents, even during the AD exacerbation period, and therefore may improve drug adherence. Maintenance of the remission period after discontinuation of the drug and the possibility of lowering the steroid class should be further studied.

## CONCLUSIONS

The cream containing a steroid and pseudo-ceramide that forms a lamellar structure not only showed anti-inflammatory effects but also greatly improved barrier function in patients with mild to moderate AD within a short period. This cream should be useful in AD, which is complicated by inflammation and reduced barrier function.

## ACKNOWLEDGEMENTS

We appreciate the staff at Dermalabo Co., Ltd. for their cooperation during the study.

**Funding.** This study was fully funded by Kao Corporation, Japan. The journal's Rapid Service Fee was also sponsored by Kao Corporation, Japan.

**Authorship.** All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

**Author Contributions.** All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Keita Okoshi, Yoshinori Kinugasa, Takuji Kume, Tsuyoshi Seki, and Azumi Nagasawa. The first draft of the manuscript was written by Yoshinori Kinugasa and Shotaro Ito; all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

**Disclosures.** Keita Okoshi, Yoshinori Kinugasa, Shotaro Ito, Takuji Kume, Tsuyoshi Seki, Takahiro Nishizaka, Joji Okada, Hiromitsu Kawada, Azumi Nagasawa, Makoto Iijima, Masatoshi Abe, and Osamu Nemoto have nothing to disclose

**Compliance with Ethics Guidelines.** The human study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The study was reviewed and approved by the Review Board of Kao Corporation (Tokyo, Japan) and Medical Corporation Kojinkai Sapporo Skin Clinic (Sapporo, Japan). All participants provided informed consent prior to inclusion in the study.

**Data Availability.** The data generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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