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Improvement effects of tapinarof on the skin barrier function in Japanese patients with atopic dermatitis

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Background: Tapinarof is a nonsteroidal, topical, aryl hydrocarbon receptor agonist. Tapinarof has been shown to be efficacious and have acceptable safety profile in the treatment of atopic dermatitis (AD).

Objective: We sought to evaluate the improvement effect of tapinarof on skin barrier function in patients with AD.

Methods: This was an open-label, uncontrolled, single-center study. Japanese patients aged ≥20 years with AD (N = 30) were included in this study. Patients applied tapinarof cream 1% once daily to the target areas on the volar forearm for 8 weeks. The primary endpoints were changes from baseline in stratum corneum hydration (SCH) and transepidermal water loss (TEWL) at the target affected area at week 8.

Results: The mean SCH value at the target affected area was 13.656 AU at baseline, 16.904 AU at week 4, and 16.423 AU at week 8. The SCH at the target affected area significantly increased from baseline to week 8, with a mean change of 2.826 AU (p = 0.0433). The mean TEWL value at the target affected area was 17.35 g/m^2/hr at baseline, 10.01 g/m^2/hr at week 4, and 9.52 g/m^2/hr at week 8. The TEWL at the target affected area significantly decreased from baseline to week 8, with a mean change of −8.03 g/m^2/hr ($p < 0.0001$). Clinical signs of AD at the target affected area were improved over time. No serious, severe, or treatment-related AEs were reported.

Conclusion: Treatment with tapinarof led to an increase in SCH and a decrease in TEWL in patients with AD, indicating the potential improvement effect of tapinarof on skin barrier function.

KEYWORDS

aryl hydrocarbon receptor (AhR), atopic dermatitis, clinical trial, stratum corneum hydration (SCH), skin barrier, tapinarof, transepidermal water loss (TEWL)

Introduction

Atopic dermatitis (AD) is a common, chronic, inflammatory skin disease [1]. The lifetime prevalence of AD is estimated to be >15% in many countries [2]. Quality of life of patients with AD is markedly affected by visible skin lesions and sleep disturbance due to persistent intense itching [3, 4]. The pathogenesis of AD is multifactorial, involving abnormal immune responses, genetic and environmental factors, and skin barrier dysfunction [5–7]. Type 2 helper T (Th2) cytokines, such as interleukin (IL)-4 and IL-13, play an important role in the development of AD [2]. Skin barrier dysfunction in AD is associated with loss-of-function mutations in the gene of filaggrin, a critical skin barrier-related protein in the stratum corneum [8, 9]. The expression of skin barrier-related proteins can be downregulated by Th2 cytokines, which are overexpressed in AD skin lesions, leading to further skin barrier dysfunction [8, 9]. Compared to healthy skin, a decrease in stratum corneum hydration (SCH) and an increase in transepidermal water loss (TEWL) are noted at AD skin lesions [10], which reflects less hydrated skin resulting from the barrier dysfunction in patients with AD.

The primary goal of treatment of AD is to maintain a long-term remission in which signs and symptoms of AD are absent or minimal without disturbance of daily activities [1]. Topical corticosteroids are the mainstay of current treatment of AD; however, long-term use of topical corticosteroids is associated with specific adverse reactions such as skin atrophy and may cause skin barrier dysfunction [11]. Although nonsteroidal topical drugs become available, there remains a need for efficacious topical drugs that can be used long-term and improve skin barrier function.

Tapinarof is a non-steroidal, topical aryl hydrocarbon receptor (AhR) agonist [12]. The AhR is a cytosolic ligand-dependent transcription factor. By activating AhR, tapinarof upregulates the expression of skin barrier-related proteins, such as filaggrin, hornerin, and involucrin [12]. The pharmacological action of tapinarof also includes downregulation of the proinflammatory cytokine expression and upregulation of the antioxidative enzyme expression through activation of the nuclear factor erythroid 2 related factor 2 pathway [12, 13]. Thus, tapinarof can be a novel topical drug for AD with characteristic pharmacological actions including the potential for improvement of skin barrier function.

To date, several clinical studies to evaluate the efficacy and safety of tapinarof have been conducted in patients with AD [14–17]. These study results revealed that tapinarof was efficacious and had acceptable safety profile. In the present study, we sought to evaluate the improvement effect of tapinarof on skin barrier function in patients with AD.

Methods

Study design

This was an open-label, uncontrolled, single-center (Hosui General Medical Clinic, Hokkaido, Japan) study in which Japanese patients with AD (N = 30) received tapinarof cream 1% once daily for 8 weeks (Figure 1). Patients visited the study site at 2, 4, and 8 weeks after initiation of treatment. This study was approved by an institutional review board (Sapporo Skin Clinic Institutional Review Board) and was conducted in compliance with the guidelines for Good Clinical Practice and the Declaration of Helsinki. This study is registered in Japan Registry of Clinical Trials (jRCT, https://jrct.niph.go.jp/), with the registration number of jRCT2011210062.

Study population

This study enrolled Japanese patients aged ≥20 years with a clinical diagnosis of AD according to the criteria of the Japanese Dermatological Association [1]. Eligible patients had a target affected area of approximately ≥25 cm^2 on the left or right volar forearm, an Investigator's Global Assessment (IGA, Supplementary Table S1) score of 3 (moderate) or 4 (severe) at the target affected area, a target unaffected area of approximately ≥25 cm^2 on the same volar forearm as for the target affected area, and a SCH value of ≤25 (in arbitrary unit, AU) and a TEWL value of ≥9 $g/m^2/hr$ at the target affected area. Exclusion criteria were summarized in the Supplementary Material. Healthy volunteers aged ≥20 years (N = 10) were also enrolled in this study to obtain reference data of SCH and TEWL values and did not receive study treatment. A target area on the left or right volar forearm in each healthy volunteer was determined by the investigator. All patients and healthy volunteers provided written informed consent to participate in this study.

Study treatment

Patients were instructed to apply a thin layer of study treatment once daily to the target areas (target affected area and target unaffected area) throughout the 8-week treatment period. Therapies that may have interfered with study assessments were prohibited during the study (e.g., biologic agents, phototherapy at the target areas, and topical agents at the target areas; Supplementary Material for details).

Study assessments

The primary endpoints were changes from baseline in SCH and TEWL at the target affected area at week 8. The

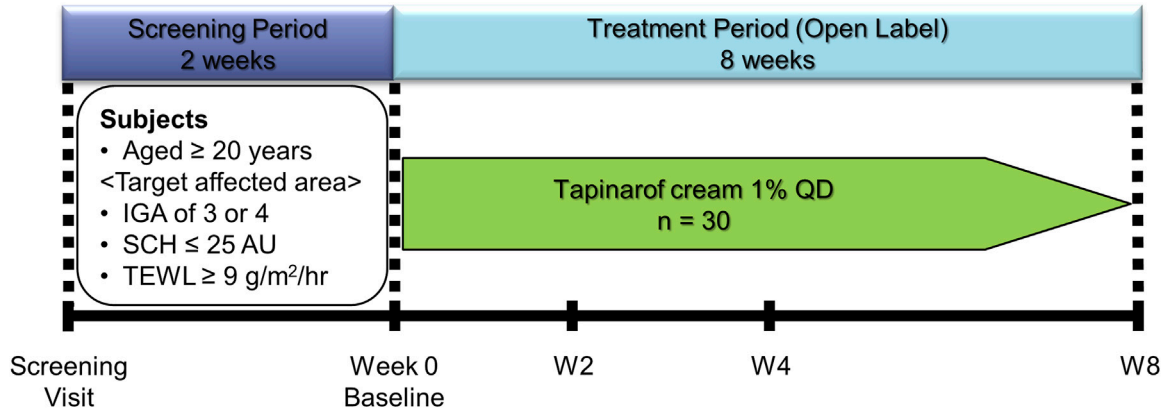

FIGURE 1
Study Design. AD, atopic dermatitis; AU, arbitrary unit; IGA, Investigator's Global Assessment; QD, once daily; SCH, stratum corneum hydration; TEWL, transepidermal water loss.

TABLE 1 Demographics and baseline characteristics.

	Patients with AD (N = 30)	Healthy volunteers (N = 10)
Age (years)	36.3 (10.6)	36.7 (13.6)
Sex [n (%)]		
Male	12 (40.0)	5 (50.0)
Female	18 (60.0)	5 (50.0)
Duration of AD (years)	29.2 (9.7)	—
SCH (AU)	13.656 (4.811)[a]	30.590 (8.934)
TEWL (g/m²/hr)	17.35 (7.92)[a]	5.97 (1.84)
IGA score[a] [n (%)]		
3 (moderate)	28 (93.3)	—
4 (severe)	2 (6.7)	—
Severity score[a]	8.03 (1.58)	—

Data are displayed as mean (SD) unless otherwise indicated. Healthy volunteers were enrolled in this study to obtain reference data of SCH and TEWL values and did not receive study treatment.
AD, atopic dermatitis; AU, arbitrary unit; IGA, Investigator's Global Assessment; SCH, stratum corneum hydration; SD, standard deviation; TEWL, transepidermal water loss.
[a]These were assessed at the target affected area in patients with AD.

measurement of SCH at the target areas was performed with Corneometer® CM825 (Courage+Khazaka electronic GmbH, Cologne, Germany). The measurement of TEWL at the target areas were performed with Tewameter® TM300 (Courage+Khazaka electronic GmbH, Cologne, Germany). The patients and healthy volunteers were kept at rest for at least 20 min in a constant temperature and humidity room before the measurement of SCH and TEWL. The severity of AD at the target affected area was assessed with IGA and severity scores. The IGA score was a static 5-point morphological assessment of overall disease severity from 0 (clear) to 4 (severe) (Supplementary Table S1). The severity score corresponded to the clinical sign score in Eczema Area and Severity Index [18], rating the severity of each of four clinical signs (erythema, infiltration/papulation, excoriation, and lichenification) on a 6-point scale (0 = none, 1 = mild, 1.5 = mild to moderate, 2 = moderate, 2.5 = moderate to severe, 3 = severe), and the overall score ranged from 0 to 12. Safety assessments included the incidence and severity of adverse events (AEs).

Statistical analyses

The sample size calculation was based on the data from a study of delgocitinib ointment, where SCH and TEWL values

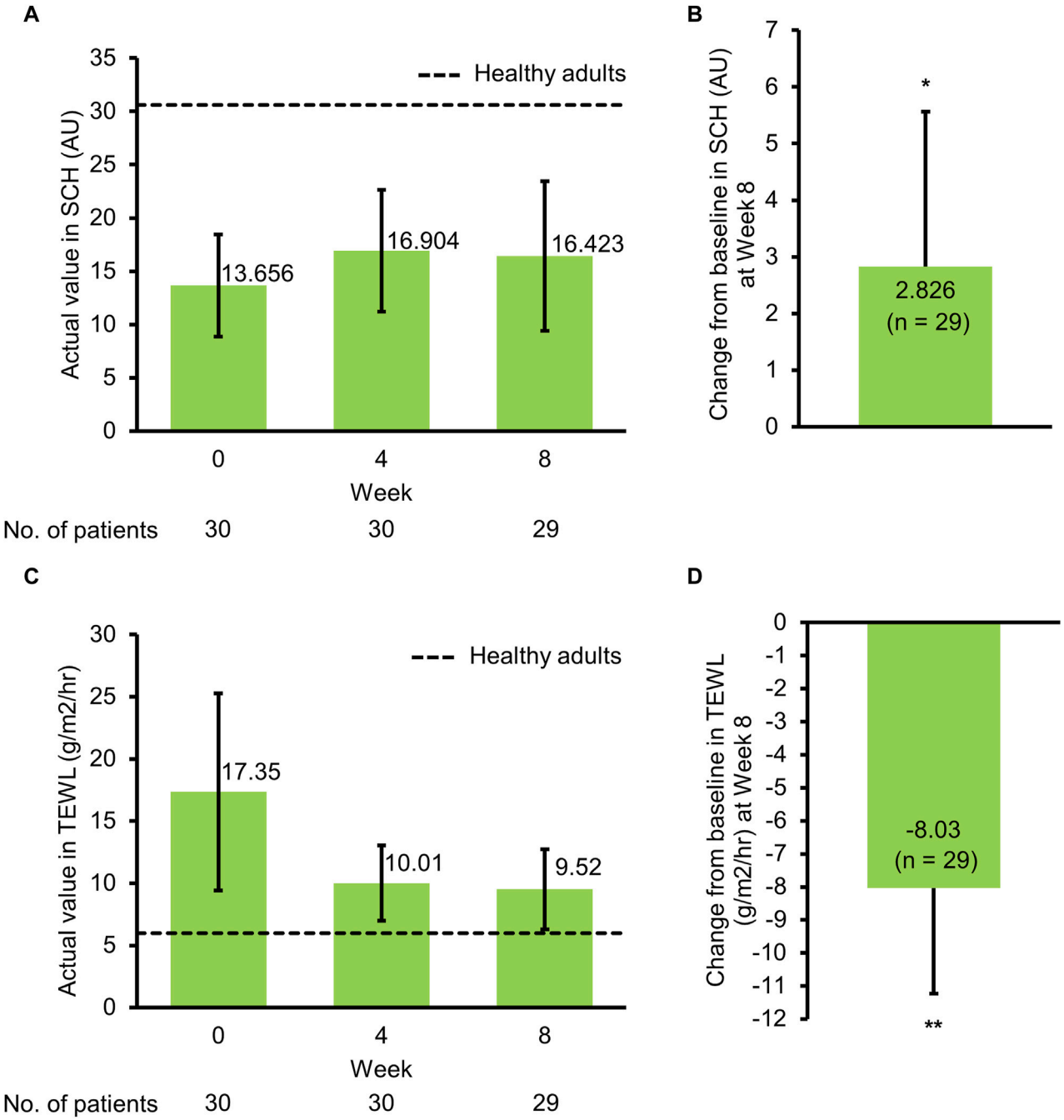

FIGURE 2
Effects on skin barrier functions in patients with atopic dermatitis. **(A)** Actual value (mean ± SD) in SCH by study visit, **(B)** change from baseline (mean + 95% CI) in SCH at Week 8, **(C)** actual value (mean ± SD) in TEWL by study visit, **(D)** change from baseline (mean – 95% CI) in TEWL at Week 8. AU, arbitrary unit; CI, confidence interval; SCH, stratum corneum hydration; SD, standard deviation; TEWL, transepidermal water loss. *$p = 0.043$, **$p < 0.0001$ (t-test).

were evaluated in patients with AD [19]. A sample size of 30 was determined to have sufficient power for analysis of the primary endpoints with a 2-sided t-test at the 5% significance level, with at least 99.9% power for SCH and 88.8% power for TEWL. The primary analyses of efficacy (SCH, TEWL, IGA, and severity score) used the full analysis set (FAS), which included all patients who underwent the assessment of efficacy at least once after initiation of study treatment. Mean changes from baseline in SCH and TEWL were calculated by study visit, and the t-test was performed at week 8 for the mean changes

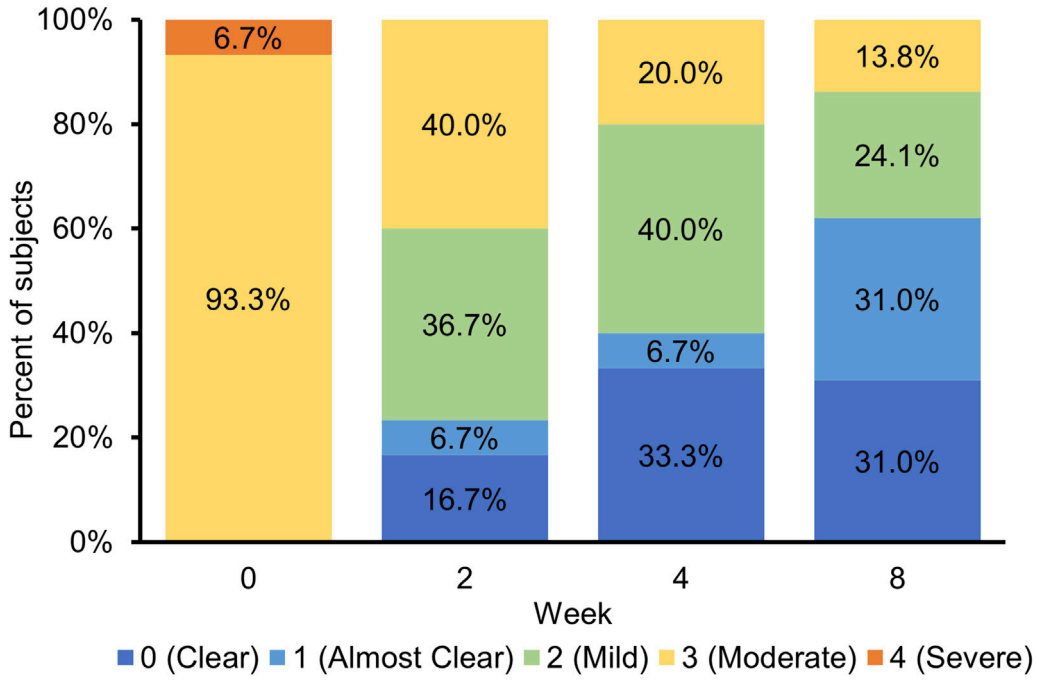

FIGURE 3
Frequency distribution of investigator's global assessment (IGA) scores by study visit.

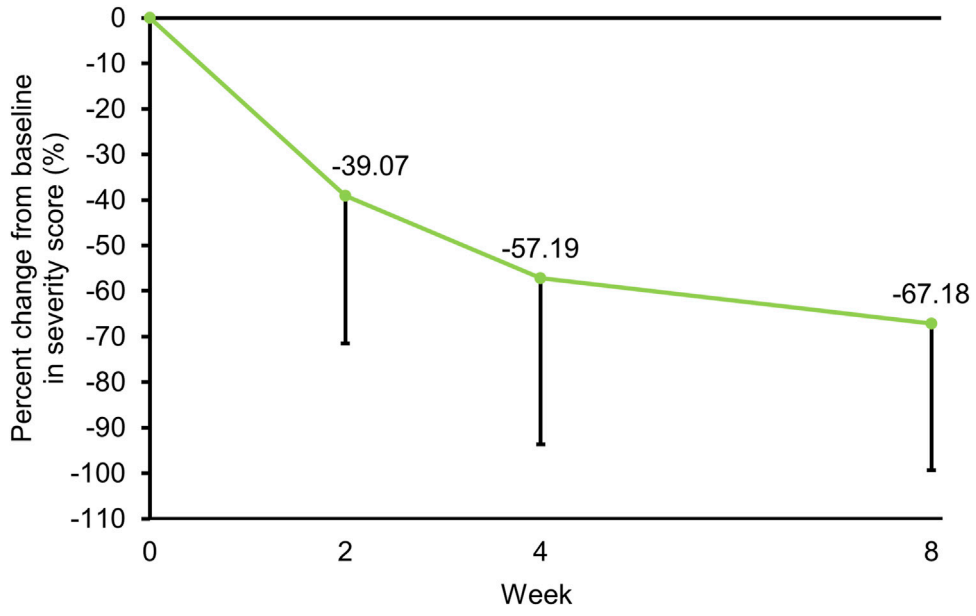

FIGURE 4
Percent change (mean – SD) from baseline in severity score over time. SD, standard deviation.

from baseline at the target affected area. No adjustment was performed for multiple tests. The frequency distribution of IGA scores was generated by study visit. The mean percent change from baseline in severity score was calculated by study visit. The safety analyses used the safety analysis population, which included all patients who underwent

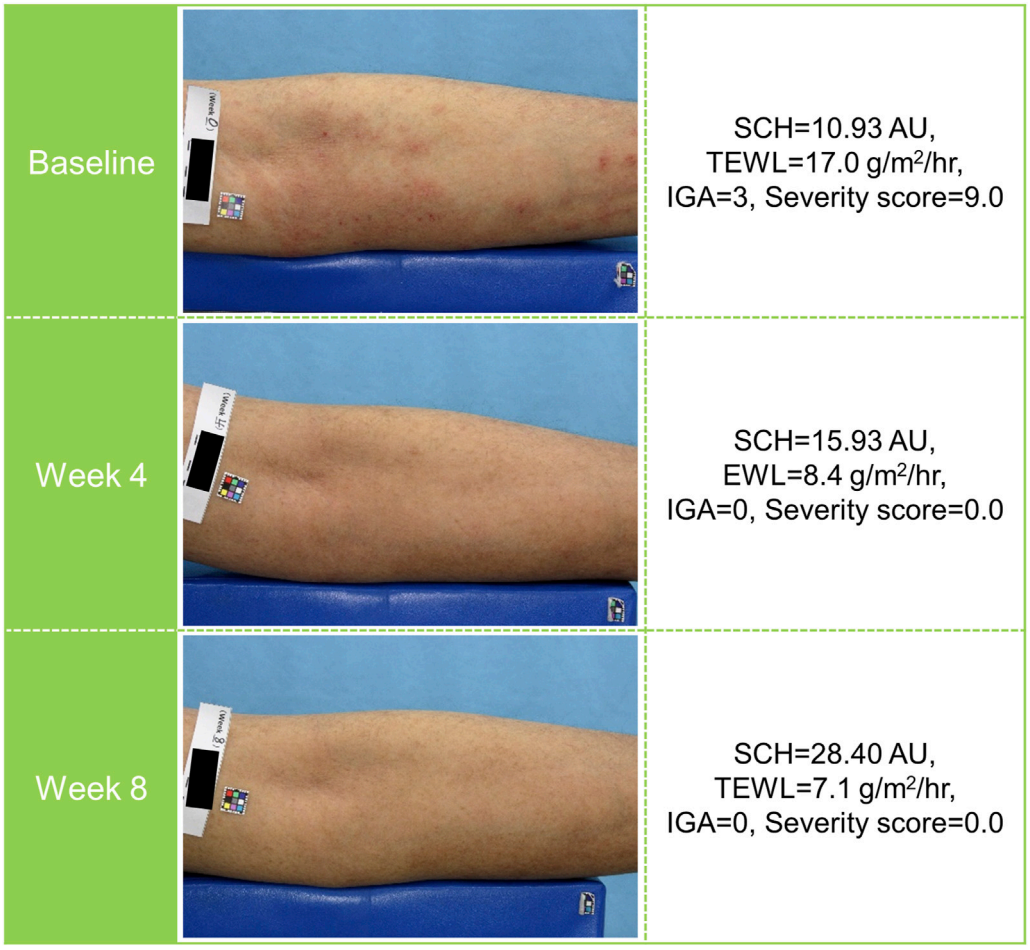

FIGURE 5
Representative clinical images of a patient receiving tapinarof. AU, arbitrary unit; IGA, Investigator's Global Assessment; SCH, stratum corneum hydration; TEWL, transepidermal water loss.

the assessment of safety at least once after initiation of study treatment.

Results

Study population

A total of 30 patients with AD received study treatment, and 29 patients completed the 8-week treatment. One patient was discontinued from the study because of an AE. In addition, 10 healthy volunteers were enrolled in the study. The mean age and sex distribution in patients with AD were similar to those in healthy volunteers. Patients with AD had less hydrated skin than healthy volunteers, as indicated by baseline SCH and TEWL values. Approximately 90% of patients with AD had a baseline IGA score of 3 (moderate) at the target affected area (Table 1).

Efficacy

The mean SCH value at the target affected area was 13.656 AU at baseline, 16.904 AU at week 4, and 16.423 AU at week 8 (Figure 2A; Supplementary Table S2). The SCH at the target affected area significantly increased from baseline to week 8, with a mean change of 2.826 AU (95% confidence interval [CI], 0.091 to 5.561 AU; $p = 0.0433$) (Figure 2B; Supplementary Table S2). The mean TEWL value at the target affected area was 17.35 g/m^2/hr at baseline, 10.01 g/m^2/hr at week 4, and 9.52 g/m^2/hr at week 8 (Figure 2C; Supplementary Table S2). The TEWL at the target affected area significantly decreased from baseline to week 8, with a mean change of −8.03 g/m^2/hr (95% CI, −11.23 to −4.83 g/m^2/hr; $p < 0.0001$) (Figure 2D; Supplementary Table S2).

The IGA score at the target affected area was improved over time. Approximately 60% of patients achieved an IGA score of 0 (clear) or 1 (almost clear) at week 8 (Figure 3). The severity score

TABLE 2 Adverse events.

	Patients with AD (N = 30)
AEs	5 (16.7)
COVID-19	1 (3.3)
Folliculitis	1 (3.3)
Hordeolum	1 (3.3)
Lymphadenitis	1 (3.3)
Toxic skin eruption[a]	1 (3.3)
Serious AEs	0
Severe AEs	0
Treatment-related AEs	0
AEs leading to study discontinuation	1 (3.3)

Data are displayed as number of subjects (%). The AE terms reported by the investigator were coded using MedDRA V.24.1.
AD, atopic dermatitis; AE, adverse event; COVID-19, coronavirus disease 2019; MedDRA, medical dictionary for regulatory activities terminology.
[a]The toxic skin eruption was a skin reaction observed not only at the application site but also at non-application sites. The event led to study discontinuation, but the investigator considered that it was not related to the study treatment.

at the target affected area decreased over time. The mean percent change from baseline in severity score was −57.19% at week 4 and −67.18% at week 8 (Figure 4; Supplementary Table S3). Representative clinical images of the target affected area are presented in Figure 5.

Safety

Adverse events were reported in 5 of 30 (16.7%) patients (Table 2). No serious, severe, or treatment-related AEs were reported. One patient was discontinued from the study because of a moderate AE of toxic skin eruption.

Discussion

This study was conducted to evaluate the improvement effect of tapinarof applied once daily for 8 weeks on skin barrier function in patients with moderate or severe AD. At baseline, patients with AD had lower SCH and higher TEWL values than healthy volunteers (Table 1), which was in agreement with results of recent clinical studies [10, 19]. There appeared to be a difference in SCH and TEWL between baseline and week 4, although no statistical tests were performed. At week 8, SCH and TEWL at the target affected area were significantly improved from baseline (Figures 2B, D), indicating the potential improvement effect of tapinarof on skin barrier function. No apparent differences in SCH and TEWL values were found between week 4 and week 8 (Figures 2A, C), whereas AD clinical signs, as assessed with IGA and severity scores, were improved from baseline through week 8 (Figures 3, 4). Given that the clinical efficacy of tapinarof tended to increase over 52 weeks of treatment [20], treatment with tapinarof beyond 8 weeks can further improve skin barrier function in patients with AD.

Non-steroidal topical drugs have become available for the treatment of AD. In contrast to topical corticosteroids, topical calcineurin inhibitors do not cause skin atrophy [1]. Topical calcineurin inhibitors have been reported to have a different effect on skin barrier function from that of topical corticosteroids [21–24]. Recently approved topical drugs such as Janus kinase inhibitors and phosphodiesterase 4 inhibitors have been shown to upregulate the expression of skin barrier proteins, including filaggrin and loricrin [25, 26]. Tapinarof also upregulates these skin barrier proteins by a different mechanism of action via AhR activation [12]. The upregulation effect of tapinarof on skin barrier proteins was enhanced in combination with a Janus kinase inhibitor [27]. Combination treatment with tapinarof and other topical drugs may provide a better improvement effect on skin barrier function in patients with AD.

This study was in an open-label manner without any treatment control group, which limited the interpretation of data. It is uncertain whether there are any differences in improving skin barrier function between tapinarof and other topical drugs. Treatment with tapinarof in this study was 8-week short duration, whereas patients with AD generally require long-term treatment. Longer treatment duration should be considered to evaluate the durability of improvement effect on skin barrier function, which can contribute to long-term maintenance of remission in AD. Additionally, this study included only Japanese patients; therefore, the improvement effect of tapinarof on skin barrier function is uncertain in non-Japanese patients, who potentially have different phenotypes of AD [28, 29]. In clinical studies including non-Japanese patients, however, tapinarof demonstrated the clinical efficacy in the treatment of AD [14, 15, 17], indicating that tapinarof is most likely to show the improvement effect on skin barrier function in non-Japanese patients.

In summary, 8-week treatment with tapinarof led to an increase in SCH and a decrease in TEWL in patients with AD. Clinical signs of AD were improved over time. No new safety concerns emerged. The potential improvement effect of tapinarof on skin barrier function can be beneficial in the long-term maintenance of remission in AD.

Data availability statement

The datasets presented in this article are not readily available because the participants of this study did not give written consent for their data to be shared publicly, so due to the sensitive nature of the research supporting data is not available. Requests to access the datasets should be directed to RM, ryusei.murata@jt.com.

Ethics statement

The studies involving humans were approved by Sapporo Skin Clinic Institutional Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

All authors contributed to the study concept and design, the conduct of the study, and data interpretation. RM and SF drafted the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

AI received advisory board honoraria, consulting fees or speaker honoraria from AbbVie, Eli Lilly Japan, Japan Tobacco, Maruho, Novartis, Sanofi, LEO pharma, and Torii Pharmaceutical, and received research grants from AbbVie, Eli Lilly Japan, Japan Tobacco, Novartis, Otsuka Pharmaceutical, Amgen, and Sanofi. GT received a research grant and consulting fee from Japan Tobacco. RM, SF, and SY are employees of Japan Tobacco Inc.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/jcia.2024.13418/full#supplementary-material

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