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Clinical effect of delgocitinib 0.5% ointment on atopic dermatitis eczema intensity and skin barrier function

Masatoshi Abe MD, PhD[1] | Hajime Iizuka MD, PhD[2] | Ikue Nemoto-Hasebe MD, PhD[3] | Osamu Nemoto MD, PhD[1] | Hiroyuki Toyama MS[4] | Katsuyo Ohashi-Doi PhD[4] | Kenji Kabashima MD, PhD[5]

[1]Kojinkai Sapporo Skin Clinic, Sapporo, Japan

[2]Research Institute of Psoriasis, Sapporo, Japan

[3]Kojinkai Housui General Medical Clinic, Sapporo, Japan

[4]Medical affairs Department, TORII Pharmaceutical Co Ltd, Tokyo, Japan

[5]Department of Dermatology, Graduate School of Medicine, Kyoto University, Kyoto, Japan

Correspondence
Katsuyo Ohashi-Doi, Ph.D, Medical affairs department, TORII Pharmaceutical Co Ltd, 3-4-1, Nihonbashi-Honcho, Chuo-ku, Tokyo 103-8439, Japan.
Email: katsuyo.doi@torii.co.jp

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Abstract

Objectives: Delgocitinib is a small-molecule JAK inhibitor that has recently been approved in Japan as the world's first topical JAK/STAT pathway inhibitor for the treatment of atopic dermatitis (AD). In this study, the effects of delgocitinib 0.5% ointment treatment on skin rash severity and skin-barrier function were examined.

Methods: Adult Japanese patients with mild-moderate AD (n = 23) were recruited into the trial. Healthy subjects (n = 10) were examined in parallel. The effects of four weeks of treatment with delgocitinib 0.5% ointment on the partial eczema area and severity index (pEASI) score, stratum corneum hydration (SCH), and trans-epidermal water-loss (TEWL) were examined. Patient reported effects of the treatment were assessed by a questionnaire.

Results: Four weeks of treatment showed a statistically significant improvement ($p < .001$) in pEASI score of 61.8%, ±54.0 (mean%, SD) compared to baseline in AD patients. Improvement in SCH at four weeks (37.6AU, ±11.5 (mean, SD), $p < .001$) was achieved in AD patients compared to baseline (SCH = 24.9AU, ±8.8 (mean, SD)). A trend toward reduction in TEWL over time was seen in the active treatment group (TEWL = 9.1 g/h/m^2 at baseline, 7.1 g/h/m^2 at two weeks, and 6.9 g/h/m^2 at 4 weeks). The pEASI score and SCH and TEWL values improved from two-to-four weeks treatment. Patients reported perceived improvements after four weeks of treatment on all parameters associated with skin condition. No safety concerns were identified.

Conclusions: Treatment with delgocitinib 0.5% ointment was well tolerated and showed improvements of both eczema and SCH in adult AD patients.

KEYWORDS
atopic dermatitis, delgocitinib ointment, Janus kinase inhibitor, skin barrier function, stratum corneum hydration

1 | INTRODUCTION

Atopic dermatitis (AD) is a common and usually chronic inflammatory skin disease that affects 15–30% of children and 2–10% of adults in industrialized countries.[1] AD is a complex disease that typically develops in early childhood in genetically susceptible individuals with a predisposition of atopic diseases (e.g., allergic rhinitis, food allergy, allergic asthma), characterized by a strong T helper 2 (Th2) immune response. Multiple Th2 cytokines play important roles in AD pathogenesis, most prominently IL-4, IL-5, IL-13, IL-33, and thymic stromal lymphopoietin (TSLP).[2] An additional dominant genetic risk factor of AD is loss-of-function mutations in the filaggrin gene (*FLG*) which causes disruption of the epidermal barrier and leads to increased skin permeability and water loss.[3] Disruption of the skin barrier allows penetration of the skin by allergens which contributes to maintain and exacerbate the pathology of AD through expression of the pro-inflammatory cytokine TSLP produced, e.g., by keratinocytes and skin-resident dendritic cells.[4,5]

AD includes three predominant manifestations: visibly inflamed red skin, skin dryness caused by skin-barrier disruption and pruritus. These three manifestations originate from the general pathophysiology of AD and are linked by common immunological pathways in a way that contributes to the continued maintenance of the diseased state of the skin. Skin barrier integrity may be compromised innately as a result of *FLG* mutations in affected individuals, but an acquired reduction in *FLG* expression may occur as a consequence of keratinocytes developing in the presence of the pro-inflammatory Th2 cytokines IL-4 and IL-13.[6,7] Pruritus can follow as a consequence of the dryness of AD-affected skin patches but may also occur as a result of the proinflammatory Th2 milieu of AD where IL-31 and TSLP are known to cause pruritus by acting directly on sensory neurons in the skin.[4,7,8] The mechanical stress applied to the skin when scratched by the patient in response to pruritus may subsequently promote further lesion of the affected skin, resulting in increased TSLP expression which, in turn, enhances inflammation.[4,9]

The cytokines that are responsible for the debilitating manifestations of AD and for maintaining the underlying pathogenic immunological conditions of the disease are attractive targets for therapeutic intervention.[10] The activity of cytokines related to AD and other autoimmune diseases can be inhibited by different means, e.g., by preventing the binding of the cytokines to their cognate cell-surface expressed receptors by cytokine-specific monoclonal antibodies (mAbs).[11] mAbs targeting proinflammatory cytokines have been successfully used for systemic treatment of atopic skin conditions including AD[11] but the use of mAbs for topical administration has not been widely successful due to the challenges of formulation and delivery.[12] Alternatively, rather than preventing extracellular cytokine/receptor binding, the activity of cytokines can be inhibited by blocking the intra-cellular signal transduction pathways that relay the signal from the cell-surface bound cytokine receptor to the nucleus. The cytokines responsible for the development and maintenance of AD rely on signal transduction by the JAK/STAT signaling pathway.[13] Upon binding of a cytokine to its receptor, the receptor dimerizes, which allows the binding of JAK or TYK2 kinases to the intracellular part of the receptor followed by phosphorylation of both the receptor and the JAK/TYK2 proteins themselves. Subsequently, STAT proteins are recruited to the receptor/JAK or receptor/TYK2 complex where they become activated by phosphorylation, and upon dimerization translocate to the nucleus where they promote the transcription of genes encoding, e.g., AD-related proinflammatory cytokines such as IL-4, IL-13, and IL-31.

Delgocitinib is a small-molecule JAK inhibitor that has recently been approved in Japan as the world's first topical JAK/STAT pathway inhibitor for the treatment of AD. In non-clinical studies, delgocitinib exhibited beneficial effects on three prominent factors of AD in the form of anti-inflammatory and anti-pruritic effects and improvement of skin barrier function.[14–18] Efficacy and safety of delgocitinib have been reported in clinical studies in adult AD patients[1,19–21] as well as pediatric AD patients.[22,23] In clinical studies, anti-inflammatory and anti-pruritic effects have been reported, but so far, reports of skin barrier improvement as a result of delgocitinib treatment have been lacking.

The purpose of this study was to examine the clinical effects of delgocitinib 0.5% ointment in adult patients with mild-to-moderate AD. Efficacy variables included skin rash severity as well as skin barrier integrity measured as the variables stratum corneum hydration (SCH) and trans-epidermal water loss (TEWL). To evaluate the improvement of skin barrier function, changes in SCH and TEWL were measured in AD patients as change from baseline at timepoint (after two weeks and four weeks of treatment).

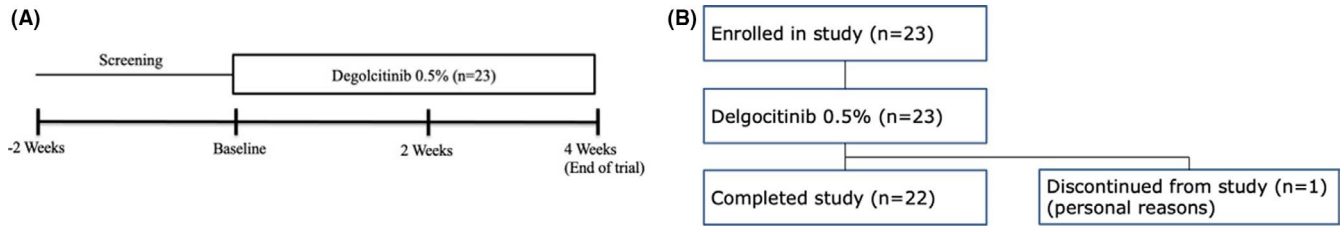

FIGURE 1 (A) Trial design. 23 subjects were treated with delgocitinib 0.5% ointment for four weeks. Efficacy assessments were made at baseline and after two and four weeks of treatment. Ten control subjects were included in the study but did not receive any treatment. (B) Subject disposition. One subject in the active treatment group left the trial prior to completion for personal reasons

2 | METHODS

2.1 | Study design

An investigator-initiated, single-center, open label study of delgocitinib 0.5% ointment was conducted in adult Japanese patients with mild-to-moderate AD to examine the improvement of eczema severity and skin-barrier function after twice-daily topical administration of the drug over the four-week study period. The study included 23 patients with atopic dermatitis who visited the Hosui General Medical Clinic from November 2020 to February 2021. The overall trial design is shown in Figure 1A.

2.2 | Study patients

Japanese patients ≥20 years of age at the time of informed consent who were available for outpatient treatment and who complied with the following criteria were eligible to participate in the study: (1) diagnosis of AD prior to informed consent according to the "Definition and diagnostic criteria for atopic dermatitis" by the Japanese Dermatological Association. Exclusion criteria included: (1) active infection of the planned drug application skin area at baseline (2) crust-forming ulcers or erosions at the planned drug application site at baseline (3) diagnosis of the following diseases at the during the screening period and/or at baseline: (I) Kaposi's varicelliform eruption (II) scabies (III) molluscum contagiousm (IV) impetigo contagious (V) psoriasis (VI) disorders (Netherton syndrome, etc.) presenting with ichthyosiform erythroderma (VII) collagen disease, such as SLE and dermatomyositis (VIII) contact dermatitis (IX) other skin disorders on the planned drug application area, which can affect evaluation (4) use of biological products (cytokines, antibody drugs, etc.) within 24 weeks prior to baseline (5) use of the following drugs within 28 days prior baseline: (I) systemic adrenocortical steroid, in oral, injectable, suppository, and inhaled forms (II) systemic immunosuppressants (III) live vaccines (6) use of the following therapies within 28 days prior to baseline: (I) phototherapy (UVB, Narrow-band UVB, PUVA, etc.) (II) allergen immunotherapy/allergen desensitization therapy (7) application of the “strongest” or “very strong” strength of topical corticosteroids[21,24] (corresponding to class I and II, i.e., “very high” and “high,” respectively, in the USA[25]) on the observation area within 14 days prior to baseline (8) application of delgocitinib 0.5% ointment, topical tacrolimus ointment, “strong,” “medium,” or “weak” topical corticosteroids[21,24] corresponding to class III to VII i.e., “medium” to “lowest,” respectively, in the USA[25] or moisturizer on the observation area within seven days prior to baseline (9) severe complications involving brain, liver, kidney, heart, lung, digestive system, blood, endocrine system, metabolic system, or mental system (10) history of severe drug allergies such as anaphylactic shock (11) history of drug addiction or alcoholism (12) suspicion of pregnancy, pregnancy, and/or breastfeeding at baseline (13) malignant tumors or a history of malignant tumors within five years from the beginning of the screening period (14) participation in other trials including medical devices or clinical studies with intervention within 12 weeks prior to baseline (15) history of side effects of delgocitinib 0.5% ointment treatment (16) the patient was determined by the investigator to be unsuitable for the study.

2.3 | Study treatment

Delgocitinib 0.5% ointment was applied to the observation site twice daily in an appropriate amount up to 5 g per application. The observation site was determined by the physician in charge of the patient at baseline.

2.4 | Study variables

AD patients were examined at the clinic at three time-points: at baseline, week two and week four. At each visit, the following efficacy assessments were made: (1) pEASI was scored on a scale of 0–12 points, dividing skin symptoms into four categories: erythema, infiltrates/papules, scratch marks, and lichenification. Each category was scored on a six-point scale (0: none, 1: mild, 1.5: between mild and moderate, 2: moderate, 2.5: between moderate and severe, 3: severe) (2) Stratum corneum hydration (SCH) was measured for the site of observation with a Corneometer CM825 (Courage & Khazaka, Cologne, Germany) under constant temperature and humidity (3) trans-epidermal water loss (TEWL) was measured in a thermo-hydrostatic chamber using a Tewameter TM300 (Courage & Khazaka, Cologne, Germany). For SCH and TEWL, the measurements were performed after the subject was acclimated for at least 20 min in a thermo-hygrostatic chamber (room temperature 20 ± 2°C, humidity 50±3%). (4) Each of the following items were evaluated by a questionnaire on a scale from 0 to 10:

1. Skin dryness score (0: dry, 10: moist).
2. Texture of the skin score (0: rough, 10: smooth).
3. Elasticity of skin score (0: no elasticity, 10: greatest imaginable elasticity).
4. Itchy skin score (0: maximum imaginable itch, 10: no itch).
5. Skin appearance score (0: maximum imaginable appearance is poor, 10: maximum imaginable appearance is good).
6. Satisfaction with treatment score (0: not satisfied at all, 10: satisfied).

Safety assessments were conducted by interviewing AD patients for subjective symptoms, and by medical examination (auscultation, percussion, visual examination, palpation, etc.).

The skin condition of ten healthy subjects without atopic dermatitis were assessed at baseline, and the following evaluations were conducted using the same procedures as for the AD study patients: (1) SCH (2) TEWL (3) questionnaire (questions 1–5).

TABLE 1 Demographics and baseline characteristics

	Control group ($N = 10$) n(%)	Delgocitinib 0.5% ointment ($N = 23$) n(%)
Sex		
Male	4 (40.0)	7 (30.4)
Female	6 (60.0)	16 (69.6)
Age (years)		
Mean ± SD	34.7 ± 8.0	35.0 ± 8.4
Median	35.5	35.0
Min-max	24.0–46.0	20.0–51.0
Observation sites		
Right forearm	5 (50.0)	17 (73.9)
Left forearm	5 (50.0)	6 (26.1)
Pre-study drug use		
Applicable	0 (0.0)	21 (91.3)
Not applicable	10 (100.0)	2 (8.7)
pEASI SCORE		
Mean ± SD	–	5.96 ± 2.09
Median	–	6.00
Min-max	–	2.00–10.00
SCH		
Mean ± SD	33.95 ± 9.49	24.92±8.75
Median	32.60	24.40
Min-max	16.30–47.00	9.70–47.00
TEWL		
Mean ± SD	4.561 ± 0.914	9.131±6.818
Median	4.650	8.600
Min-max	3.270–5.760	2.750–37.210

Abbreviations: pEASI, Partial Eczema Area and Severity Index; SCH, Stratum corneum hydration; TEWL, trans-epidermal water loss; SD, standard deviation

2.5 | Statistical analyses

Statistical analysis was done with SAS 9.4 (SAS Institute, Cary, NC, USA). Hypothesis testing was two-tailed at a 5% level of significance. Summary statistics and 95% confidence intervals (CI) of the means were calculated at baseline, two weeks, and four weeks, respectively, for SCH and TEWL. A Paired-samples t-test was performed for the mean values of SCH and TEWL at four weeks.

In the questionnaire, summary statistics and 95% CI of the mean values were calculated for baseline and four weeks. In addition, Wilcoxon's signed rank test was performed on the results of the questionnaire from baseline to four weeks.

3 | RESULTS

3.1 | Trial population

The disposition of study patients is shown in Figure 1B. Of the 23 patients recruited into the study, 22 completed the four-week treatment with twice daily application of delgocitinib 0.5% ointment. One patient left the study prior to completion for personal reasons unrelated to the treatment (Figure 1B). Demographics and baseline characteristics are summarized in Table 1. Demographic parameters such as age and sex were comparable in the two groups. There was no recorded pre-study AD drug use in the control group, but in the delgocitinib treatment group, pre-study drug use was reported for the majority (91.3%) of the subjects in agreement with the AD condition of this group. The baseline values of the two main efficacy variables relating to skin barrier function, SCH and TEWL, differed between the two groups as expected, reflecting study-relevant differences between the AD patients and the control group (Table 1).

3.2 | Efficacy endpoints

3.2.1 | Eczema severity

The change in pEASI score in the active treatment group at two and four weeks, respectively, compared to baseline is shown in Figure 2. After treatment with delgocitinib 0.5% ointment for two weeks, a statistically significant ($p < .001$) difference in the pEASI score of

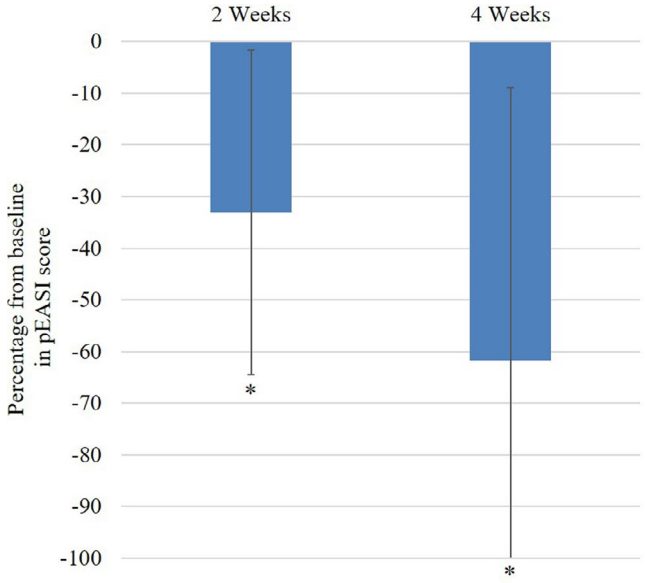

FIGURE 2 Percent change from baseline in partial eczema area and severity index (pEASI) score over time (mean ± SD). *$p < .001$ (paired-samples t-test delgocitinib 0.5% ointment vs baseline)

−31.8%, ±32.2 (mean%, SD) compared to baseline was seen. After four weeks of treatment, the statistically significant difference relative to baseline persisted, and the numerical difference to baseline had increased to −61.8%, ±54.0 (mean%, SD) (Figure 2).

3.2.2 | Clinical presentation

A representative example of the clinical presentation of AD-related skin lesions before and after four weeks of delgocitinib 0.5% ointment treatment is shown in Figure 3. At baseline, the inflamed condition of the skin was clearly evident (Figure 3A). After four weeks of treatment, inflammation was no longer visible (Figure 3B).

3.2.3 | Skin barrier function

The effect of treatment with delgocitinib 0.5% ointment on skin barrier function in AD subjects was measured by the two parameters SCH and TEWL (Figure 4). In AD patients, a statistically significant increase ($p < .05$) in the level of stratum corneum hydration from an SCH value of 24.9 AU, ±8.8 (mean, SD) at baseline to an SCH value of 30.5, ±12.0 (mean, SD) after two weeks treatment with delgocitinib 0.5% ointment was seen. After four weeks of delgocitinib 0.5% ointment treatment, the level of hydration measured in AD patients had increased further to an SCH value of 37.6 AU, ±11.5 (mean, SD), demonstrating a highly statistically significant increase in SCH compared to baseline ($p < 0.001$) (Figure 4A). At baseline, the mean SCH level in AD patients was statistically significantly different from the control groups.

For TEWL, a statistically significant difference was seen between the control group and the AD patient group at baseline (Figure 4B).

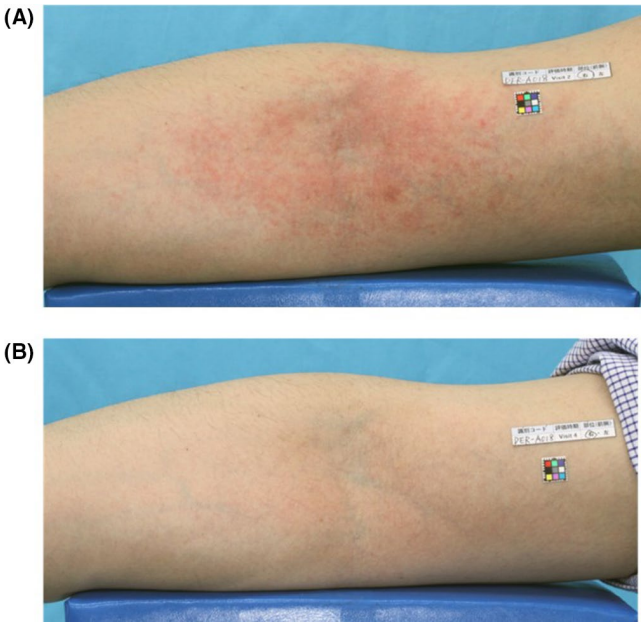

FIGURE 3 Clinical improvement of patients after four weeks of delgocitinib 0.5% ointment treatment. (representative example) (A) symptoms at baseline, (B) symptoms after four weeks

In the AD patient group, there was a gradual numerical decrease in the mean TEWL from 9.1 g/h/m^2 at baseline to 7.1 g/h/m^2 at two weeks ($p = .206$) and 6.9 g/h/m^2 at four weeks ($p = .179$, baseline vs four weeks) after delgocitinib 0.5% ointment treatment (Figure 4B).

3.2.4 | Patient-reported outcomes (questionnaire)

Additional parameters relating to the AD patients' subjective evaluation of the status of their skin condition before and after treatment with delgocitinib 0.5% ointment were addressed by a questionnaire. AD patients were asked to fill out the questionnaire at baseline and after four weeks of treatment. The subjects in the control group were asked to fill out the questionnaire at baseline (Table 2). In the active treatment group, perceived improvements of all parameters associated with skin condition (dryness, texture, elasticity, itchiness, and general appearance) as well as the overall satisfaction with treatment were reported. For all parameters, statistically significant ($p < .001$, four weeks vs baseline) improvements were achieved (Table 2). After four weeks of delgocitinib 0.5% ointment treatment, the mean values of the self-reported skin condition scores in the AD group approached the mean values of the scores obtained from the control group (Table 2).

3.2.5 | Safety

Safety data were collected from all AD patients enrolled in the study (Table 3). One patient (4.3%) reported two local adverse events (application site erythema and application site itching). Both were restricted to the site of application and were mild in severity, and both resolved without sequelae (Table 3).

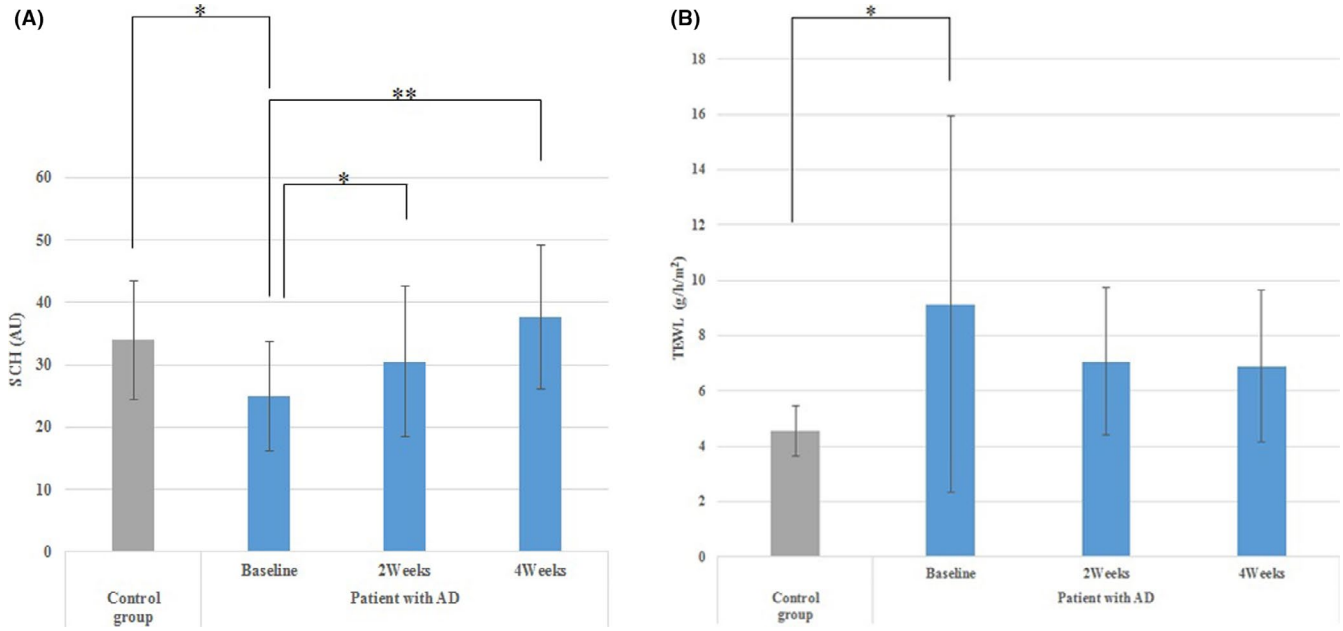

FIGURE 4 Effects of delgocitinib 0.5% ointment treatment on skin barrier functions in control group (baseline values) and in AD patients (baseline, after two weeks and after four weeks of treatment) (A) effect on SCH (B) effect on TEWL. SCH, stratum corneum hydration; TEWL, trans-epidermal water loss; AD, atopic dermatitis; SD, standard deviation; AU, arbitrary units, $^{**}p < .001$, $^{*}p < .05$ (paired-samples *t*-test delgocitinib 0.5% ointment vs baseline)

TABLE 2 Patient-reported outcomes

	Patient with AD		Wilcoxon signed-rank test[a]	Reference Control group (*N* = 10)
	Baseline (*N* = 23)	4 Weeks (*N* = 22)		
Skin dryness score				
Mean ± SD	3.9 ± 1.0	7.3 ± 1.4		8.5 ± 1.1
Median	4.0	8.0	$p < .001$	8.5
Score min–max	2.0–5.0	4.0–9.0		7.0–10.0
Texture of the skin score				
Mean ± SD	4.0 ± 1.3	7.3 ± 1.6		8.7 ± 1.6
Median	4.0	7.5	$p < .001$	9.0
Score min–max	2.0–7.0	4.0–10.0		6.0–10.0
Elasticity of skin score				
Mean ± SD	3.8 ± 1.2	6.9 ± 1.6		8.5 ± 1.3
Median	4.0	7.0	$p < .001$	8.5
Score min–max	0.0–5.0	4.0–10.0		7.0–10.0
Itchy skin score				
Mean ± SD	3.9 ± 1.6	7.5 ± 1.6		9.7 ± 0.9
Median	4.0	7.5	$p < .001$	10.0
Score min–max	2.0–7.0	5.0–10.0		7.0–10.0
Skin appearance score				
Mean ± SD	4.0 ± 1.1	6.8 ± 1.7		9.1 ± 1.0
Median	4.0	7.0	$p < .001$	9.0
Score min–max	2.0–6.0	4.0–10.0		7.0–10.0
Satisfaction with treatment score				
Mean ± SD	3.8 ± 1.7	7.9 ± 2.0		–
Median	4.0	8.0	$p < .001$	–
Score min–max	0.0–9.0	4.0–10.0		–

Abbreviation: AD, atopic dermatitis; SD, standard deviation.

[a]Four weeks vs baseline.

TABLE 3 Summary of adverse events

Adverse drug reaction		*n* (%)	Events
General disorders and administration site conditions	1	(4.3)	2
Application site erythema	1	(4.3)	1
Application site itching	1	(4.3)	1

Note: Data are displayed as number of patients (%) and number of events. Safety set included all AD patients ($N = 23$).

4 | DISCUSSION

This was an investigator initiated clinical study that addressed the efficacy and safety of delgocitinib 0.5% ointment in patients with mild-to-moderate AD. The actively treated group of AD patients and the control group were well matched regarding sex and age (Table 1). The two groups differed regarding baseline values of SCH and TEWL in agreement with the AD status of the subjects in the active treatment group (Table 1). Only two drug related adverse events were reported in a single patient and both were mild in severity, indicating that delgocitinib 0.5% ointment treatment was well tolerated in patients with mild-to-moderate AD.

Efficacy variables included two of the main clinical manifestations of AD, skin inflammation and skin barrier function. Skin inflammation was measured as change from baseline of the pEASI score. The pEASI score is the investigator's clinical assessment of the severity of AD and is one of the best validated outcome measures of AD.[26] The effect of delgocitinib 0.5% ointment treatment obtained in this study was time dependent as the effect on the pEASI score increased over the treatment period from −31.8% compared to baseline after two weeks of treatment to −61.8% after four weeks of treatment (Figure 2). In patients with mild-to-moderate AD, reduction in pEASI score of 61.8% as seen after four weeks of treatment would correspond to reduction of one AD severity category, e.g., from "moderate" to "mild" or "mild" to "almost clear,"[26] supporting a clinically relevant effect of delgocitinib 0.5% ointment treatment.

The compromised skin barrier function seen in AD patients that may develop as a consequence of a genetic disposition in the *FLG* gene as well as of the Th2 pro-inflammatory milieu that down-regulates filaggrin production and impairs the natural development of keratinocytes is a critical manifestation of the disease. Restoring the skin barrier function in AD patients would prevent access of allergens through the skin that otherwise contribute to the perpetuation of inflammation and prevent skin dryness by minimizing trans-epidermal water loss. From in-vitro micro-array analyses of gene expression patterns in a reconstituted human skin model, IL-4 and IL-13 expression was shown to have a negative impact on the expression of genes involved in keratinocyte differentiation and downregulated epidermal differentiation through JAK/STAT signaling, supporting the importance of the JAK/STAT pathway in AD.[15] Using pre-clinical in-vivo mouse models of AD with or without concomitant inflammation and a human skin transplantation model, delgocitinib was shown to decrease TEWL and promote the expression of the epidermal cell protein loricrin, filaggrin, and the filaggrin-derived natural moisturizing factor (NMF) that is essential for appropriate stratum corneum hydration, both in mice and in transplanted human skin.[15] In this study, the association between delgocitinib treatment and improvement of skin barrier integrity was supported by the findings that treatment with delgocitinib 0.5% ointment achieved statistically significant improvements in SCH compared to baseline in a time-dependent manner over two and four weeks of treatment (Figure 4A). Further support for skin-barrier improvement after delgocitinib 0.5% ointment treatment was provided by the TEWL analyses that showed numerical decrease of the mean TEWL values over time, although statistical significance of the magnitude of changes compared to baseline was not achieved (Figure 4B). The lack of statistically significant changes in TEWL may be attributable to the small sample population in this study and the fact that the baseline TEWL values in the AD group was relatively low. In addition to the objective improvements on AD by delgocitinib 0.5% ointment that was demonstrated by the physician-assessed pEASI score and the SCH and TEWL measurements, subjective assessments of improvements as experienced by the patients were done by questionnaire. The patients' own assessments of treatment effect contribute to ascertain if the outcomes of a treatment can be defined as clinically meaningful. When the actively treated AD patients in this study were asked about their opinion on several parameters relating to the skin condition at the site of delgocitinib application (moisture, texture, elasticity, general appearance, level of itchiness), the combined responses showed statistically significant improvements on all parameters, including general satisfaction with treatment, after four weeks of treatment with delgocitinib compared to baseline (Table 2). In addition to providing relief from the debilitating symptoms of AD already from two to four weeks, the general satisfaction with delgocitinib treatment seen in this study is likely to improve patient adherence during long-term treatment.

For the management of AD, delgocitinib offers improved treatment attributes over the more traditional treatment options like topical corticosteroids and calcineurin inhibitors regarding key factors. While topically applied corticosteroids are safe and effective for short-term treatment of AD, prolonged treatment may lead to skin atrophy and concomitant skin barrier damage.[13,27–29] A contributing factor for the decrease in skin thickness and concomitant impairment of the skin barrier seen after corticosteroid treatment is reduction in the tight-junction proteins claudin 1 (Cldn-1) and claudin 4 (Cldn-4).[27] Cldn-1 and Cldn-4 play a crucial role for the maintenance of the epidermal barrier and unlike corticosteroids, treatment with delgocitinib 0.5% ointment showed no reduction in the expression of these tight-junction proteins, even after prolonged treatment.[27] Topical corticosteroids may be less effective toward improvements of SCH[29] but have been shown to reduce AD-associated TEWL[29] although reduction in TEWL may be indirectly caused by concomitant corticosteroid-mediated vasoconstriction[30] or reduction of

inflammation.[28] Calcineurin inhibitors such as tacrolimus are also commonly used for treatment of AD with impaired skin barrier function[28,29] and are effective for increasing SCH and reducing TEWL.[13,28–31] No direct evidence of mechanism has been reported, and the rescue of skin barrier function by calcineurin inhibitors may be indirect effects caused by improvement of skin inflammation.[31]

Skin atrophy was not seen with delgocitinib 0.5% ointment treatment of adult AD patients even after 52 weeks of treatment.[21] Improvements of skin barrier functions after treatment with delgocitinib was shown pre-clinically to occur independently of coexisting inflammation by a mechanism that actively promotes the production of FLG and NMF.[15]

Limitations to this trial include small sample size, the open trial design, and lack of a placebo control. The results of the questionnaire may be biased because this is a single-arm open study. Also, other reports have shown that the baseline TEWL value in AD patients is around 20–30 g/h/m^2.[29,32] In this study, no inclusion criteria for TEWL were defined, so patients with a TEWL of about 9.1 g/h/m^2 were recruited. Consequently, skin barrier function could not be accurately assessed by TEWL because of the narrow range of improvement. Well-defined inclusion criteria for TEWL should be integrated in future studies. A possible limitation of this study is the treatment time of only four weeks. Longer treatment times, e.g., eight weeks or more, will be considered for future studies.

Regarding the statistically significant increase in SCH, it remains to be confirmed whether the observed increase is based on increases in FLG and NMF by delgocitinib 0.5% ointment treatment.

In summary, skin barrier disruption is a key event in the establishment and maintenance of AD. Restoration of skin barrier function is an important aspect of effective AD treatment as it will protect against penetration of external pro-inflammatory stimuli such as allergens, and consequently reduce inflammation and itching, and improve skin hydration. In this study, treatment with delgocitinib 0.5% ointment was well tolerated and showed improvement of both eczema and SCH in adult AD patients.

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DECLARATION SECTION

Approval of the research protocol: The protocol for this research project has been approved by a suitably constituted Ethics Committee of the institution and it conforms to the provisions of the Declaration of Helsinki. The study protocol was approved by the Clinical Research Review Committee of the Hattori Clinic Medical Corporation.

Informed consent: All informed consent was obtained from the subjects.

Registry and the Registration No. of the study/trail: The study outline was registered and published in the Japan Registry of Clinical Trials (trial ID no. jRCTs031200160).

Animal Studies: N/A.

CONFLICT OF INTERESTS

HT and KOD are employees of Torii Pharmaceutical Co., Ltd. MA has received speaker's honoraria from Maruho, Kyowa Kirin, AbbVie, Eli Lilly, Novartis, Sanofi and Torii Pharmaceutical. KK received grants from Japan Tobacco Inc., Kyowa Kirin, LEO Pharma, Maruho, Mitsubishi Tanabe Pharma, Ono Pharmaceutical, Sun Pharma, Procter & Gamble Company, Taiho Pharma and Torii Pharmaceutical. HI, INH, ON have no conflict of interest. KK is a member of the Journal of Cutaneous Immunology and Allergy Editorial Board. Management of the peer review process, and all editorial decision making, for this article was undertaken by Editor in Chief.

ORCID

Hiroyuki Toyama https://orcid.org/0000-0002-4756-8520

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