ORIGINAL ARTICLE

Delgocitinib ointment in pediatric patients with atopic dermatitis: A phase 3, randomized, double-blind, vehicle-controlled study and a subsequent open-label, long-term study

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Background: Delgocitinib 0.5% ointment, a topical Janus kinase inhibitor, has been approved in Japan for adult patients with atopic dermatitis (AD).

Objective: To evaluate the efficacy and safety of delgocitinib ointment in pediatric patients with AD.

Methods: Part 1 of this study was a 4-week double-blind period in which Japanese patients aged 2 through 15 years were randomized in a 1:1 ratio to delgocitinib 0.25% ointment or vehicle ointment. Part 2 was a 52-week extension period. Eligible patients entered part 2 to receive 0.25% or 0.5% delgocitinib ointment.

Results: At the initiation of the study, approximately half of the patients had moderate AD. At the end of treatment in part 1, the least-squares mean percent change from baseline in modified Eczema Area and Severity Index score, the primary efficacy endpoint, was significantly greater for delgocitinib ointment than for vehicle (−39.3% vs +10.9%, $P < .001$). In part 2, improvements in AD were also seen through week 56. Most adverse events were mild and unrelated to delgocitinib across the study periods.

Limitations: Only Japanese patients were included. In part 2, no control group was included and rescue therapy was allowed.

Conclusion: Delgocitinib ointment was effective and well tolerated when applied to Japanese pediatric patients with AD for up to 56 weeks. (J Am Acad Dermatol https://doi.org/10.1016/j.jaad.2021.06.014.)

Key words: atopic dermatitis; delgocitinib; eczema; Janus kinase; JAK inhibitor; JTE-052; ointment; pediatric patients; pruritus; skin barrier; topical therapy.

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INTRODUCTION

Atopic dermatitis (AD) is a chronic, inflammatory skin disease characterized by eczematous lesions and intense pruritus,[1-3] with a higher prevalence in children (up to 25%) than in adults (7% to 10%).[4] AD in childhood tends to resolve with age, although some patients continue to have symptoms of AD in adulthood.[1,5]

Topical therapies form the mainstay of treatment of AD in both adults and children. Currently, topical corticosteroids and topical calcineurin inhibitors are widely used to reduce skin inflammation. Although generally safe for most patients, these drugs can cause local adverse reactions, such as skin atrophy and telangiectasia for topical corticosteroids and symptoms of skin irritation for topical calcineurin inhibitors.[1,6] Although novel drugs for AD are currently under clinical development, few of them target AD in children.[7,8] Additionally, given its chronic and relapsing course, long-term treatment of AD is generally required. Therefore, novel topical treatment options without long-term safety concerns are still needed for AD in children.

Janus kinase (JAK) inhibitors represent a new drug class for the treatment of AD.[7-9] The JAK-signal transducer and activator of transcription pathway plays an important role in exerting the biologic effects of many inflammatory cytokines, including interleukin 4, interleukin 13, and interleukin 31,[10-12] which are closely associated with the pathophysiology of AD.[13-17] Delgocitinib is a novel JAK inhibitor that has inhibitory effects on all types in the JAK family (JAK1, JAK2, JAK3, and tyrosine kinase 2).[18] It has been developed for AD in Japan by Japan Tobacco and Torii Pharmaceutical and is in development in a cream formulation for dermatologic conditions worldwide, excluding Japan by LEO Pharma. Delgocitinib 0.5% ointment was found to be clinically effective in adult patients with AD[19-21] and has been approved in Japan.[22] A 4-week phase 2 study in pediatric patients with AD demonstrated the potential effectiveness of 0.25% and 0.5% delgocitinib ointment in that patient population.[23] In the present phase 3 study, the efficacy and safety of delgocitinib ointment in Japanese pediatric patients with AD was evaluated over a 4-week double-blind period (part 1) and a 52-week extension period (part 2).

CAPSULE SUMMARY

- Delgocitinib ointment, a topical Janus kinase inhibitor, was effective and well tolerated when applied for up to 56 weeks to Japanese pediatric patients with atopic dermatitis.
- Delgocitinib ointment is a promising therapeutic option for atopic dermatitis in children as well as in adults.

METHODS

Study design

This study was conducted at 23 medical institutions in Japan in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol was approved by the institutional review boards. The study information is registered with the Japan Pharmaceutical Information Center Clinical Trials Information (identifier JapicCTI-184064).

Part 1 was a 4-week, randomized, double-blind, vehicle-controlled study in which Japanese patients aged 2-15 years with AD were randomized 1:1 to delgocitinib 0.25% ointment or vehicle ointment (Supplemental Fig 1; available via Mendeley at https://doi.org/10.17632/6yrdmwydzj.1). Randomization was stratified by age (2-6, 7-11, and 12-15 years) and investigator's global assessment (IGA) score. After completing part 1, patients could enter part 2, which was a 52-week, open-label extension study. Patients who did not complete part 1 because of worsening of AD were withdrawn from the study or entered part 2 early, at the investigator's discretion. In part 2, all patients received 0.25% or 0.5% delgocitinib ointment.

Patients

Written informed consent was obtained from the parents or guardians of the patients. Assent was obtained from patients, if possible. At initiation of part 1, patients were required to have an AD diagnosis according to the Japanese Dermatological Association criteria[1]; a modified eczema area and severity index (mEASI) score of ≥ 5, which was calculated by excluding the head/neck region score from the EASI[24] total score; an IGA score of 2 (mild), 3 (moderate), or 4 (severe); and inflammatory eczema affecting 5% to 30% of the body surface area. Exclusion criteria are summarized in the Supplemental Table I and Supplemental Fig 1.

Study treatment

In part 1, a concentration of 0.25% was selected for delgocitinib ointment. In part 2, delgocitinib ointment at a concentration of 0.5% could be used according to the patient's disease condition (eg, mEASI score ≥ 10 at initiation of part 2 or inadequate

Abbreviations used:

AD: atopic dermatitis
AE: adverse event
EASI: eczema area and severity index
EOT: end of treatment
IGA: investigator's global assessment
JAK: Janus kinase
mEASI: modified eczema area and severity index

response to the 0.25% ointment) and at the investigator's discretion. Patients were instructed to apply the study drug twice daily (maximum dose per application, 5 g) to the areas affected by inflammatory eczema, excluding dry skin areas and the scalp. Concomitant use of any therapy to the application areas was prohibited.

In part 2, topical corticosteroids and tacrolimus ointment could be used as rescue therapy, at the investigator's discretion; however, concurrent use of rescue therapy and delgocitinib ointment to the same area was prohibited. Other prohibited and permitted concomitant therapies are summarized in the Supplemental Table I and Supplemental Fig 1.

Efficacy and safety evaluations

Efficacy was evaluated based on the following parameters: mEASI, EASI, IGA, face/neck IGA, pruritus score, and percent of body surface area affected by AD. These parameters are detailed in the Supplemental Table I and Supplemental Fig 1. In part 1, the primary efficacy endpoint was the percent change from baseline in mEASI score at the end of treatment (EOT). Secondary efficacy endpoints included the proportions of patients achieving at least 50% or 75% improvement from baseline in mEASI score (mEASI-50, mEASI-75) at EOT, the proportions of patients achieving an IGA or face/neck IGA score of 0 (clear) or 1 (almost clear) with at least a 2-point improvement from baseline (IGA success, face/neck IGA success) at EOT, and the changes or percent changes from baseline in the efficacy parameters at each study visit across parts 1 and 2. Safety evaluations included the incidence and severity of adverse events (AEs), vital signs, and clinical laboratory tests. Plasma concentrations of delgocitinib were measured at selected visits.

Statistical analyses

Sample-size calculation was based on the results of a phase 2 study of delgocitinib ointment in pediatric patients with AD.[23] A sample size of 60 patients per group would yield at least 90% power to detect a significant difference between delgocitinib and vehicle groups in the primary efficacy endpoint, with a 1-sided test at the 2.5% significance level. This assumes that the mean (±standard deviation) percent change from baseline in the mEASI score would be −50% (±60%) for delgocitinib and −5% (±60%) for vehicle.

The population of patients who underwent the study-specified evaluation at least once after the start of study treatment was used in the primary analyses of efficacy, safety, and pharmacokinetics. The EOT value for efficacy evaluations was defined as the value at week 4, study discontinuation, or immediately before part 2. For long-term efficacy evaluations across parts 1 and 2, baseline (week 0) was defined as the first day of delgocitinib treatment.

Between-group differences in the least-squares percent change or change at EOT from baseline in mEASI, EASI, and pruritus scores were tested by analysis of covariance at a 1-sided significance level of 2.5%, with the baseline value as the covariate. These endpoints at other study visits were evaluated descriptively. For responder analyses of mEASI and IGA scores, Fisher's exact tests were performed at a 2-sided significance level of 5%. No formal multiple comparison adjustment was made.

RESULTS

Patients

A total of 137 patients were randomized in part 1 (Supplemental Fig 2). Of 69 patients in the delgocitinib group, 62 (89.9%) completed part 1, and 7 (10.1%) entered part 2 early. Of 68 patients in the vehicle group, 48 (70.6%) completed part 1 and 19 (27.9%) entered part 2 early, although 1 (1.5%) was withdrawn from the study. A total of 135 patients entered part 2 and 118 (87.4%) patients completed it.

No major differences between treatment groups in part 1 were found in the demographic and baseline characteristics (Table I). At initiation of part 1, approximately half of the patients had moderate AD (IGA score of 3). In part 2, approximately 80% of the patients received the 0.5% concentration of delgocitinib ointment at least once and approximately half of the patients received rescue therapy (Supplemental Table I).

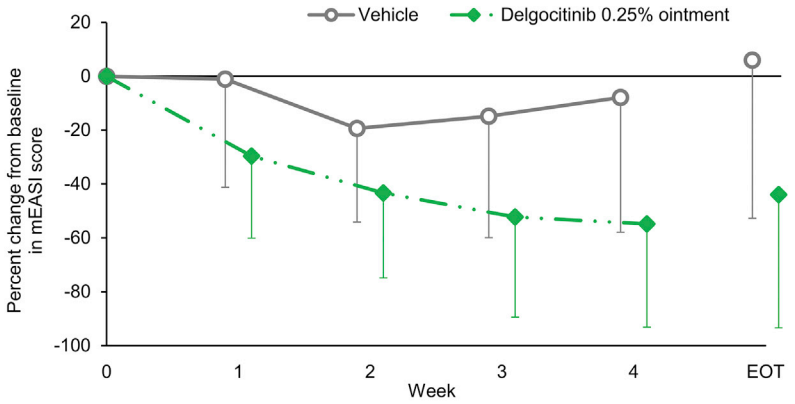
Efficacy

In part 1, the least-squares mean percent changes from baseline in the mEASI score were −39.3% in the delgocitinib group and +10.9% in the vehicle group at EOT. The reduction in mEASI score was significantly greater in the delgocitinib group ($P < .001$, Fig 1). Treatment difference from this result was similar to that from the post-hoc analysis at week 4 (Supplemental Table II). The mEASI score

Table I. Patient demographics and baseline characteristics

Characteristics	Vehicle ointment (n = 68)	Delgocitinib 0.25% ointment (n = 69)	Total (n = 137)
Age (years)	8.3 (3.7)	8.2 (3.9)	8.3 (3.8)
Age category (n [%])			
2-6 years	27 (39.7)	26 (37.7)	53 (38.7)
7-11 years	25 (36.8)	28 (40.6)	53 (38.7)
12-15 years	16 (23.5)	15 (21.7)	31 (22.6)
Sex (n [%])			
Men	31 (45.6)	39 (56.5)	70 (51.1)
Women	37 (54.4)	30 (43.5)	67 (48.9)
Duration of AD (years)	6.2 (3.7)	5.8 (3.8)	6.0 (3.7)
mEASI score	10.6 (4.2)	10.7 (4.3)	10.6 (4.2)
IGA score (n [%])			
2 (mild)	16 (23.5)	16 (23.2)	32 (23.4)
3 (moderate)	38 (55.9)	37 (53.6)	75 (54.7)
4 (severe)	14 (20.6)	16 (23.2)	30 (21.9)
Face/neck IGA score (n [%])			
0 (clear)	8 (11.8)	7 (10.1)	15 (10.9)
1 (almost clear)	2 (2.9)	11 (15.9)	13 (9.5)
2 (mild)	27 (39.7)	21 (30.4)	48 (35.0)
3 (moderate)	29 (42.6)	23 (33.3)	52 (38.0)
4 (severe)	2 (2.9)	7 (10.1)	9 (6.6)
Pruritus score			
Daytime score	2.3 (0.7)	2.3 (0.7)	2.3 (0.7)
Nighttime score	1.8 (0.7)	1.8 (0.7)	1.8 (0.7)
Percentage of BSA affected by AD	21.4 (6.3)	21.0 (6.6)	21.2 (6.4)

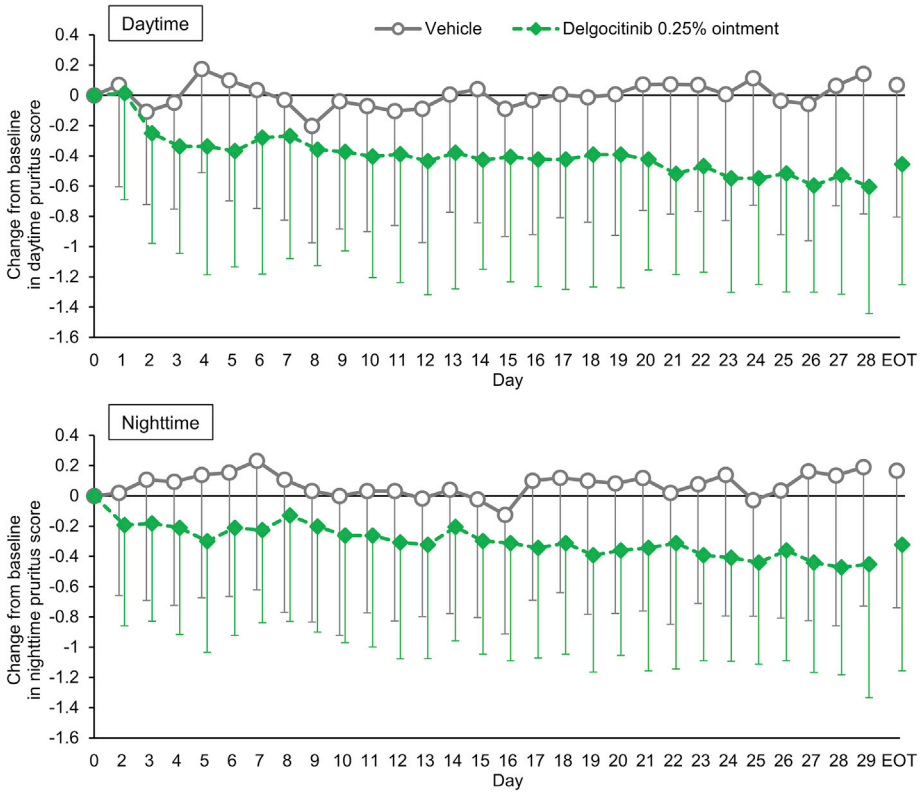
Data are displayed as mean (standard deviation) unless otherwise indicated.
AD, Atopic dermatitis; *BSA,* body surface area; *IGA,* Investigator's Global Assessment; *mEASI,* modified Eczema Area and Severity Index.



EOT	Vehicle	Delgocitinib
LS mean % change from baseline	10.9	−39.3
LS mean % difference vs vehicle		−50.2
P value vs vehicle		<.001

Fig 1. Percent change (mean − SD) from baseline in the mEASI score over time. Values obtained after use of prohibited therapies or outside the analysis visit window were excluded from analyses of weekly percent change. *EOT,* End of treatment; *LS,* least-squares; *mEASI,* modified Eczema Area and Severity Index; *SD*, standard deviation.

in the delgocitinib group was numerically reduced over time from week 1 through week 4. Representative clinical photographs show improvements at week 4 compared with baseline (Supplemental Fig 3). The delgocitinib group showed greater improvements in the other efficacy parameters at EOT, such as IGA and pruritus scores, than the vehicle group (Supplemental Tables III and IV). A numerical reduction in pruritus score was noted immediately after the start of study treatment



EOT	Vehicle	Delgocitinib
LS mean change from baseline	0.1	−0.5
LS mean difference vs vehicle		−0.6
P value vs vehicle		<.001

EOT	Vehicle	Delgocitinib
LS mean change from baseline	0.2	−0.3
LS mean difference vs vehicle		−0.5
P value vs vehicle		<.001

Fig 2. Daily change (mean − SD) from baseline in pruritus score over time. Pruritus score was a 5-point scale ranging from 0 to 4, with higher scores indicating more severe pruritus. Values obtained after use of prohibited therapies were excluded from analyses of daily change. *EOT,* End of treatment; *LS,* least-squares; *SD*, standard deviation.

in the delgocitinib group, which was maintained through week 4 (Fig 2).

In part 1, significantly greater proportions of patients achieved mEASI-50 and mEASI-75 at EOT in the delgocitinib group than in the vehicle group ($P < .001$ for both, Fig 3). An mEASI-50 was achieved by 50.7% (35 of 69) of patients in the delgocitinib group compared with 17.6% (12 of 68) of patients in the vehicle group. An mEASI-75 was achieved by 37.7% (26 of 69) of patients in the delgocitinib group compared with 4.4% (3 of 68) of patients in the vehicle group. Similarly, numerically greater proportions of patients achieved IGA success (not significant) and face/neck IGA success at EOT in the delgocitinib group than in the vehicle group ($P = .24$ for IGA success, $P = .003$ for face/neck IGA success) (Supplemental Table IV). In the delgocitinib group, the proportion of patients with an IGA score of 3 or 4 was reduced over time and that of patients with an IGA score of 0 or 1 was increased (Supplemental Fig 4).

In part 2, the improvements in mEASI, IGA, and pruritus scores were also seen through week 56 (Supplemental Fig 4 and Supplemental Table V). In patients who received delgocitinib ointment in part 1, the proportions of patients achieving mEASI-50 and mEASI-75 at week 56 were 73.6% (39 of 53) and 52.8% (28 of 53), respectively (Supplemental Fig 5). In patients who received vehicle ointment in part 1, the proportions of patients achieving mEASI-50 and mEASI-75 at week 52 were 70.5% (43 of 61) and 52.5% (32 of 61), respectively.

Safety and tolerability

In part 1, AEs were reported in 30 of 69 (43.5%) patients in the delgocitinib group and in 21 of 68 (30.9%) patients in the vehicle group (Table II). Treatment-related AEs were reported in 4 (5.8%) patients in the delgocitinib group and 1 (1.5%) patient in the vehicle group. The most common treatment-related AE in either of the treatment groups was application site folliculitis (n = 3 [4.3%]) in the delgocitinib group.

Across parts 1 and 2, AEs were reported in 115 of 134 (85.8%) patients after the start of treatment with delgocitinib ointment (Table II). Serious AEs, including 1 Kaposi's varicelliform eruption not at the application site, were reported in 6 (4.5%) patients, none of which were considered by the investigators

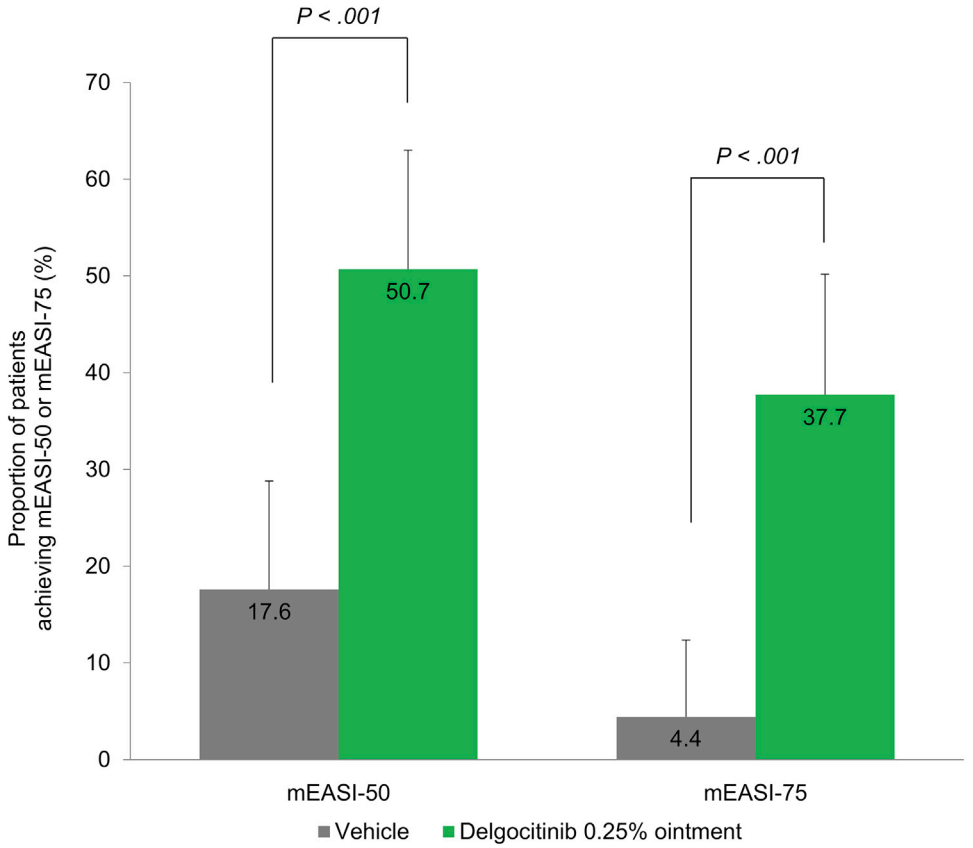


Fig 3. Proportion of patients achieving at least 50% or at least 75% improvement in mEASI score at the end of treatment. The error bars represent 95% confidence intervals. *mEASI,* Modified Eczema Area and Severity Index; *mEASI-50,* at least 50% improvement from baseline in mEASI score; *mEASI-75,* at least 75% improvement from baseline in mEASI score.

to be related to delgocitinib ointment. No severe AEs were reported. The majority of AEs were considered mild. The only 1 AE leading to study discontinuation was application site acne. The most common AE was nasopharyngitis (n = 55 [41.0%]), followed by influenza (n = 36 [26.9%]) and impetigo (n = 18 [13.4%]). The majority of AEs were considered unrelated to delgocitinib ointment, and treatment-related AEs were reported in 13 (9.7%) patients, all of which were mild.

The most common treatment-related AE was application site folliculitis (n = 4 [3.0%]). Mild application site irritation was reported in only 1 patient and no other application site symptoms, such as burning or stinging, were found. The incidence of AEs did not increase over time, except for influenza, a seasonal disease (Supplemental Table VI). The incidence of AEs under treatment with the 0.5% ointment was similar to that under treatment with the 0.25% ointment (Supplemental Table VII). No major differences in the incidence of AEs were noted between the age groups (Supplemental Table VIII).

Pharmacokinetics

No plasma concentrations of delgocitinib were detected in most patients (83.6% to 95.1%) during the study (the lower limit of quantification, 1.00 ng/mL). No major differences between study visits or between the age groups were found in the proportion of patients with detectable plasma concentrations of delgocitinib. The maximum plasma concentration of delgocitinib at each study visit ranged from 1.55 to 11.8 ng/mL (Supplemental Table IX).

DISCUSSION

In the present phase 3 study, the 4-week treatment (part 1) with delgocitinib 0.25% ointment provided clinically meaningful improvements in signs and symptoms in Japanese pediatric patients with AD. Long-term treatment for up to 56 weeks with 0.25% or 0.5% delgocitinib ointment also showed the improvement effect on AD and was well tolerated.

Delgocitinib, a pan-JAK inhibitor, broadly inhibits signaling of inflammatory cytokines involved in the pathophysiology of AD. Additionally, delgocitinib can improve skin barrier function by

Table II. Summary of adverse events

Adverse events	Vehicle-controlled period (4 weeks)		Long-term treatment period (up to 56 weeks)*
	Vehicle ointment (n = 68)	Delgocitinib 0.25% ointment (n = 69)	Delgocitinib ointment 0.25% or 0.5%* (n = 134)
AEs	21 (30.9)	30 (43.5)	115 (85.8)
Maximum severity			
Mild	20 (29.4)	28 (40.6)	92 (68.7)
Moderate	1 (1.5)	2 (2.9)	23 (17.2)
Severe	0	0	0
Treatment-related AEs	1 (1.5)	4 (5.8)	13 (9.7)
Maximum severity			
Mild	0	4 (5.8)	13 (9.7)
Moderate	1 (1.5)	0	0
Severe	0	0	0
Serious AEs	0	0	6 (4.5)
Serious treatment-related AEs	0	0	0
AEs leading to discontinuation	0	0	1 (0.7)
AEs occurring in ≥2 patients in either of the treatment groups (vehicle-controlled period) or ≥ 5% of patients (long-term treatment period)			
Nasopharyngitis	7 (10.3)	11 (15.9)	55 (41.0)
Influenza	1 (1.5)	3 (4.3)	36 (26.9)
Impetigo	1 (1.5)	0	18 (13.4)
Gastroenteritis	1 (1.5)	1 (1.4)	12 (9.0)
Conjunctivitis allergic	0	0	11 (8.2)
Upper respiratory tract infection	2 (2.9)	1 (1.4)	11 (8.2)
Fungal skin infection	0	0	10 (7.5)
Skin papilloma	0	1 (1.4)	9 (6.7)
Molluscum contagiosum	0	0	8 (6.0)
Pharyngitis	1 (1.5)	1 (1.4)	8 (6.0)
Arthropod sting	1 (1.5)	2 (2.9)	8 (6.0)
Application site folliculitis	0	3 (4.3)	7 (5.2)
Wound	0	1 (1.4)	7 (5.2)
Rhinitis allergic	0	0	7 (5.2)
Miliaria	0	0	7 (5.2)
Pyrexia	2 (2.9)	1 (1.4)	4 (3.0)
Conjunctivitis	2 (2.9)	0	3 (2.2)
Injury	2 (2.9)	0	2 (1.5)
Treatment-related AEs occurring in ≥1 patient in either of the treatment groups (vehicle-controlled period) or ≥ 1% of patients (long-term treatment period)			
Application site folliculitis	0	3 (4.3)	4 (3.0)
Application site acne	0	1 (1.4)	2 (1.5)
Molluscum contagiosum	0	0	2 (1.5)
Skin papilloma	0	1 (1.4)	1 (0.7)
Impetigo	1 (1.5)	0	1 (0.7)

Data are displayed as number of patients (%).
AEs, Adverse events.
*Patients with AEs on delgocitinib treatment across the study periods are counted; thus, data from the delgocitinib group in the vehicle-controlled period are included.

promoting the production of terminal differentiation proteins, such as filaggrin.[25] This effect of delgocitinib ointment on skin barrier function may have contributed to the positive efficacy results in the present study.

Pruritus is a distressing symptom of AD in children, leading to impairment of quality of life, such as sleep disturbance.[26] In the present study, treatment with delgocitinib ointment led to a rapid reduction in pruritus score, which was consistent with previous clinical studies with delgocitinib ointment[19,21,23] and a recent report suggesting that JAK inhibitors potentially have a direct antipruritic effect.[27,28] The antipruritic effect of delgocitinib

ointment can help reduce distress in pediatric patients with AD.

In part 2, the 0.5% ointment could be used according to the patient's disease condition (eg, mEASI score ≥ 10 or inadequate response to the 0.25% ointment). Consequently, approximately 80% of the patients received the 0.5% ointment at least once. The 0.5% ointment, which is the same strength for AD in adults, is expected to be used for AD in children in clinical practice, if deemed necessary.

Overall, delgocitinib ointment was well tolerated in pediatric patients with AD over the treatment period. Safety results in the present study were similar to those in the long-term study in adult patients with AD.[19,20] No new safety concerns with delgocitinib ointment emerged in pediatric patients with AD.

Treatment-related skin infections, including application site folliculitis and molluscum contagiosum, were all mild and the incidences were low. Systemic exposure to delgocitinib was low in all the age groups of the present study, which was consistent with previous studies in adults,[19,20] indicating that delgocitinib ointment is unlikely to pose an increased risk of systemic infections irrespective of age. Additionally, long-term treatment with delgocitinib ointment did not cause skin atrophy or telangiectasia, as reported with topical corticosteroids.[1] No strong irritation (eg, burning or stinging sensations), as reported with tacrolimus ointment,[1] was found at the application sites. Collectively, delgocitinib ointment was shown to have a favorable safety profile as a topical drug for pediatric patients with AD.

The present study has limitations. Because only Japanese patients were included, it is unclear whether the study results are applicable to non-Japanese patients who have different clinical phenotypes of AD.[14,29] Delgocitinib ointment, which targets multiple cytokine axes, is potentially effective in those populations. Additionally, in part 2, no control group was included and rescue therapy was allowed, both of which limit discussions on the long-term efficacy of delgocitinib ointment.

CONCLUSION

Delgocitinib ointment was effective and well tolerated when applied for up to 56 weeks to Japanese pediatric patients with AD. The study results indicate that delgocitinib ointment is a promising therapeutic option for AD in children as well as in adults.

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Conflicts of interest

Dr Nakagawa received consulting fees and/or speaker honoraria from Eli Lilly Japan, Japan Tobacco Inc, Kyowa Kirin, LEO Pharma, Maruho, Novartis, Torii Pharmaceutical, and UCB Japan. Dr Nemoto received advisory board honoraria and/or speaker honoraria from Japan Tobacco Inc, Kyowa Kirin, LEO Pharma, and Maruho. Dr Igarashi received advisory board honoraria, consulting fees or speaker honoraria from AbbVie, Eli Lilly Japan, Japan Tobacco Inc, Maruho, Novartis, Sanofi, LEO pharma, and Torii Pharmaceutical, and received research grants from AbbVie, Eli Lilly Japan, Pfizer, Novartis, Otsuka Pharmaceutical, Amgen Inc, and Sanofi. Dr Saeki received advisory board honoraria and/or speaker honoraria from Japan Tobacco Inc, Maruho, Taiho Pharma, Tanabe Mitsubishi, AbbVie, Sanofi and Torii Pharmaceutical, and received research grants from Maruho, Taiho Pharma, and Eisai. Dr Kabashima received consulting fees or advisory board honoraria from Chugai Pharmaceutical, Japan Tobacco Inc, Maruho, and Pola Pharma, and received research grants from AbbVie, Eli Lilly Japan, Japan Tobacco Inc, Kyorin Pharmaceutical, Kyowa Kirin, LEO Pharma, Ono Pharmaceutical, P&G Japan, Pola Pharma, Sanofi, and Tanabe Mitsubishi. Mr Oda and Mr Nagata are employees of Japan Tobacco Inc.

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