

ORIGINAL ARTICLE

# Long-term safety and efficacy of delgocitinib ointment, a topical Janus kinase inhibitor, in adult patients with atopic dermatitis

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## ABSTRACT

Previous studies demonstrated that delgocitinib ointment, a novel topical Janus kinase inhibitor, rapidly improved clinical signs and symptoms of atopic dermatitis (AD) in Japanese adult patients. We sought to evaluate the long-term safety and efficacy of delgocitinib 0.5% ointment in a 52-week study (QBA4-2). Japanese patients aged 16 years or older with AD received delgocitinib 0.5% ointment b.i.d. for up to 52 weeks. Topical corticosteroids for the treatment of worsening of AD could be used at the investigators' discretion during the treatment period. Safety end-points included the incidence and severity of adverse events (AEs). Pooled safety analyses included the data from the other long-term study (QBA4-1). Efficacy end-points included the percentage change from baseline in the modified Eczema Area and Severity Index (mEASI). A total of 506 patients were included in the pooled safety population. Overall, AEs were reported in 69.0% of patients; most AEs were mild and unrelated to delgocitinib ointment. The most common AE was nasopharyngitis, followed by contact dermatitis, acne, and application site folliculitis. No skin atrophy or telangiectasia was found at the application sites of delgocitinib ointment. Application site irritation symptoms were infrequent (<2%) and mild. The incidence of AEs did not increase over time, except for seasonal diseases. The improvement effects on AD as assessed by mEASI were maintained throughout the treatment period. Delgocitinib 0.5% ointment was well tolerated and effective when administered to Japanese adult patients with AD for up to 52 weeks.

**Key words:** atopic dermatitis, delgocitinib, Janus kinase inhibitor, long-term safety, topical.

## INTRODUCTION

Atopic dermatitis (AD) is a chronic, inflammatory skin disease accompanied by intense pruritus; the signs and symptoms of AD fluctuate with remissions and relapses.<sup>1,2</sup> Because of the chronic course of AD, long-term treatment is typically required to manage AD. Topical therapies are the mainstay of the management of AD, and topical corticosteroids and calcineurin inhibitors are widely used to reduce skin inflammation.<sup>1,3</sup> These agents, however, are associated with safety concerns. Long-term use of topical corticosteroids may lead to skin atrophy and telangiectasia.<sup>1,3</sup> Topical calcineurin inhibitors, such as tacrolimus ointment, may cause irritation symptoms including burning and stinging sensations, although these symptoms tend to decrease with AD improvement.<sup>1,3</sup> Crisaborole ointment, a phosphodiesterase 4 inhibitor, has recently been approved for mild to moderate AD in the USA,<sup>4</sup> whereas a

novel topical agent applicable to more severe AD with minimal safety concerns remains to be developed.

Delgocitinib ointment is a novel topical agent that has inhibitory effects on all types in the Janus kinase (JAK) family (JAK1, JAK2, JAK3 and tyrosine kinase 2).<sup>5</sup> The JAK–signal transducer and activator of transcription (STAT) signaling pathway plays an important role in exerting the biological effects of many inflammatory cytokines, including interleukin (IL)-4, IL-13 and IL-31.<sup>6,7</sup> Elevated production of inflammatory cytokines is associated with the pathophysiology of AD.<sup>8–13</sup> Non-clinical studies showed that topical application of delgocitinib suppresses skin inflammation,<sup>14</sup> improves the skin barrier dysfunction<sup>15</sup> and reduces pruritus<sup>16</sup> through the inhibition of cytokine signaling. In addition, early clinical studies showed the potential effectiveness of delgocitinib ointment in AD.<sup>17–19</sup>

Two phase 3 studies of delgocitinib 0.5% ointment, QBA4-1 and QBA4-2, were conducted in adult Japanese patients with

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AD. QBA4-1 consisted of a 4-week, randomized, double-blind, vehicle-controlled period (part 1) and a 24-week, open-label, extension period (part 2) (Fig. S1). In part 1, the percentage change from baseline in the modified Eczema Area and Severity Index (mEASI) score at the end of treatment, the primary efficacy end-point, was significantly greater in the delgocitinib group than in the vehicle group ( $-44.3\%$  vs  $1.7\%$ ,  $P < 0.001$ ). The improvement in the mEASI score was maintained in part 2. Most adverse events (AEs) were mild and unrelated to delgocitinib across the study periods.<sup>19</sup> Here, we report the results of QBA4-2, a 52-week open-label study, to evaluate the long-term safety and efficacy of delgocitinib ointment, along with pooled safety data from both studies.

## METHODS

### Study design

Study QBA4-2 was a 52-week open-label study (Fig. 1). The sample size ( $n = 330$ ) was selected to enable adequate evaluation of the long-term safety of delgocitinib 0.5% ointment.

This study was conducted at 47 medical institutions in Japan in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Study-related documents, including the study protocol and informed consent forms, were approved by the institutional review boards. Written informed consent was obtained from all patients. The study information is registered with Japan Pharmaceutical Information Center Clinical Trials Information ([www.clinicaltrials.jp](http://www.clinicaltrials.jp), JapicCTI-173555).

### Patients

Japanese patients aged 16 years or older and diagnosed with AD according to the criteria of the Japanese Dermatological Association<sup>1</sup> were enrolled. To be eligible to participate, patients were required to have an Investigator's Global Assessment (IGA) score between 2 (mild) and 4 (severe), and inflammatory eczema affecting 5–30% of the body surface area.

Patients with any of the following conditions were excluded: active infection at the prospective application site; cutaneous diseases likely to affect the study assessments; and mycobacterium tuberculosis, hepatitis B/C or HIV infection. Patients who had received any of the following therapies before study treatment were excluded: biologics within 24 weeks; systemic corticosteroids, systemic immunosuppressive agents, live vaccines, phototherapy and hyposensitization therapy within 28 days; and strongest or very strong topical corticosteroids<sup>1</sup> (with similar potency to class I or II [very high or high potency] corticosteroids in the USA)<sup>3</sup> within 14 days. Patients were allowed to continue to use strong or less potent topical corticosteroids<sup>1</sup> (with similar potency to class III to VII [medium to lowest] corticosteroids in the USA)<sup>3</sup> and tacrolimus hydrate ointment immediately before delgocitinib treatment. All of the therapies above were prohibited during the treatment period, except for topical corticosteroids for the treatment of worsening of AD as described below.

### Study treatment

Patients were instructed to apply delgocitinib 0.5% ointment b.i.d. to the areas affected by inflammatory eczema, excluding dry skin areas and the scalp. The maximum dose per application was limited to 5 g. Emollients, oral antihistamines and antiallergenic agents were permitted as concomitant drugs. Topical corticosteroids for the treatment of worsening of AD could be used at the investigators' discretion; however, concomitant use of delgocitinib ointment and topical corticosteroids to the same area was prohibited.

### Study assessments

Patients visited the study sites every 4 weeks, and safety was primarily assessed. Safety assessments were based on symptoms, signs, vital signs and laboratory tests. Plasma concentrations of delgocitinib were measured at selected visits, and the lower limit of quantification was 1.00 ng/mL. Efficacy assessments were based on the mEASI, IGA and pruritus Numeric Rating Scale (NRS) scores. The mEASI score, ranging 0–64.8,

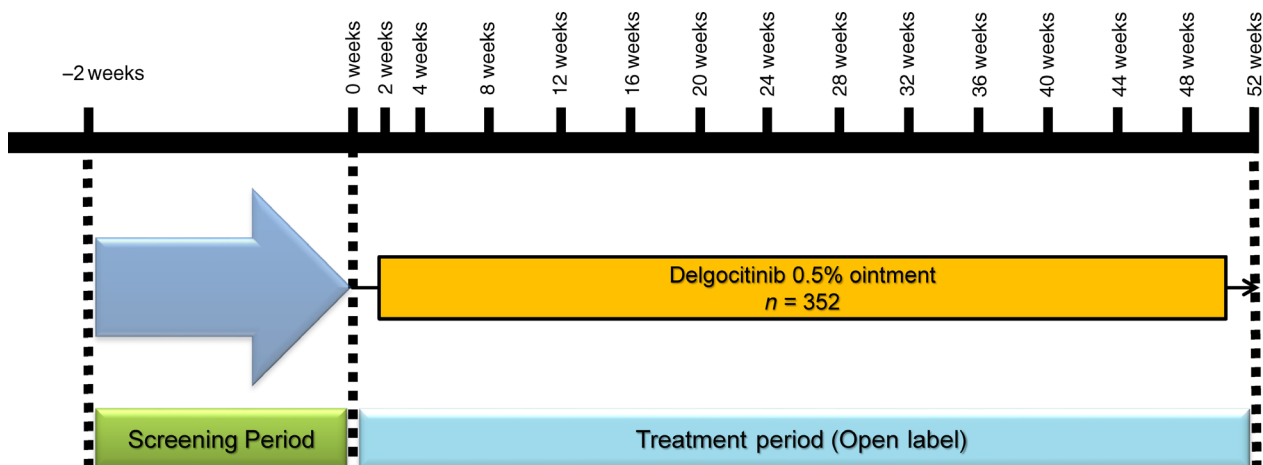


Figure 1. Study design of QBA4-2.

was calculated by excluding the head/neck region score from the EASI<sup>20</sup> total score, ranging 0–72. This modification was made to assess the treatment effect more precisely in the study where no study treatment could be applied to the scalp. The IGA score was a 6-point scale ranging from 0 (clear) to 5 (very severe) in reference to the measures of severity by the Research Group granted by the Ministry of Health, Labor and Welfare (Table S1).<sup>1</sup> The pruritus NRS score was an 11-point scale ranging from 0 (no itch) to 10 (the most severe itch), and was obtained through interview at each study visit to assess the average level of pruritus during the past 24 h.

### Statistical analyses

Analyses of safety, pharmacokinetics and efficacy were performed on the population comprising patients who underwent the respective study-specified assessments at least once after the start of delgocitinib treatment. The pooled safety population comprised all patients in this study and patients who received delgocitinib ointment in study QBA4-1.

Verbatim terms of AEs reported by investigators were coded using the Medical Dictionary for Regulatory Activities, version 19.1. For pooled safety analyses, AEs that occurred during the vehicle treatment in study QBA4-1 (i.e. AEs that occurred in the patients receiving the vehicle ointment in part 1) were not included.

For efficacy analyses, the mean change or percentage change from baseline was calculated in the mEASI, IGA and pruritus NRS scores. In the mEASI score, the proportions of patients who achieved 50% or more (mEASI-50) and 75% or more (mEASI-75) improvements from baseline were also calculated.

## RESULTS

### Patients

In study QBA4-2, of the 352 patients who received delgocitinib ointment, 262 (74.4%) completed the study (Table 1). A total of 506 patients were included in the pooled safety population. The most common reason for early study discontinuation was worsening of AD ( $n = 45$  [12.8%] in QBA4-2,  $n = 56$  [11.1%] in the pooled safety population).

At baseline, more than half of the patients had moderate AD ( $n = 215$  [61.1%] in QBA4-2,  $n = 304$  [60.1%] in the pooled safety population; Table 2). The mean duration of exposure to delgocitinib ointment was longer in study QBA4-2 (286.7 days) than in the pooled safety population (251.3 days), which reflects the difference in the treatment duration between the studies (52 weeks for QBA4-2 vs up to 28 weeks for QBA4-1). Because of worsening of AD, topical corticosteroids were used at least once by more than half of the patients ( $n = 224$  [63.6%] in QBA4-2,  $n = 288$  [56.9%] in the pooled safety population) during the treatment period. In study QBA4-2, the proportion of patients by baseline IGA score who used topical corticosteroids was the following: 2 (mild), 27.2%; 3 (moderate), 63.8%; and 4 (severe), 8.9%. The proportion of those who did not was the following: 2 (mild), 38.3%; 3 (moderate), 56.3%; and 4 (severe), 5.5%. The patients who used topical corticosteroids appeared to have more severe AD than the patients who did not. In the pooled

**Table 1.** Patient disposition

	QBA4-2 ( $n = 352$ )	Pooled safety population ( $n = 506$ )
Patients who completed the study	262 (74.4)	400 (79.1)
Patients who discontinued the study	90 (25.6)	106 (20.9)
Adverse event	16 (4.5)	17 (3.4)
Worsening of atopic dermatitis	45 (12.8)	56 (11.1)
Withdrawal by patient	23 (6.5)	26 (5.1)
Protocol deviation	1 (0.3)	1 (0.2)
Lost to follow-up	2 (0.6)	3 (0.6)
Physician decision	3 (0.9)	3 (0.6)

Data are displayed as number of patients (%). The pooled safety population includes all patients in QBA4-2 and patients who received delgocitinib ointment in QBA4-1.

safety population, however, no apparent difference in baseline IGA score was found (data not shown).

### Safety and tolerability

Overall, AEs were reported in 349 of the 506 patients (69.0%) in the pooled safety population (271/352 [77.0%] in QBA4-2; Table 3). All AEs were mild or moderate, except one severe AE of rectal cancer, which was considered unrelated to delgocitinib ointment. Most AEs were considered unrelated to delgocitinib ointment, and treatment-related AEs were reported in 78 patients (15.4%). Serious AEs occurred in seven patients (1.4%), and one serious AE of Kaposi's varicelliform eruption was considered related to delgocitinib ointment, which developed on day 26. Delgocitinib ointment had not been applied to the area where the event initially developed. Subsequently, the event expanded to the application site of delgocitinib ointment and was resolved on day 38 by withdrawal of delgocitinib ointment and an antiviral therapy. Study discontinuations due to AEs occurred in 17 patients (3.4%), and the most common AEs leading to study discontinuation were contact dermatitis in five patients (1.0%) and application site irritation in three (0.6%).

In the pooled safety population, the most common AE was nasopharyngitis ( $n = 131$  [25.9%]), followed by contact dermatitis ( $n = 23$  [4.5%]), acne ( $n = 22$  [4.3%]), application site folliculitis ( $n = 18$  [3.6%]), influenza ( $n = 17$  [3.4%]), Kaposi's varicelliform eruption ( $n = 17$  [3.4%]), application site acne ( $n = 16$  [3.2%]) and herpes simplex ( $n = 15$  [3.0%]) (Table 4). The most common treatment-related AEs were application site events such as application site folliculitis ( $n = 12$  [2.4%]) and application site acne ( $n = 11$  [2.2%]) (Table 5). The incidence of AEs did not increase over time, except for seasonal diseases such as allergic conjunctivitis and seasonal allergy (these two were mostly related to Japanese cedar pollinosis),<sup>21</sup> and influenza (Table 6). Application site irritation symptoms (irritation, pruritus, warmth or pain) were reported in less than 2% of the patients, were all mild and occurred mostly in the first 2 weeks of delgocitinib treatment.

**Table 2.** Baseline patient characteristics, extent of exposure to delgocitinib ointment and concomitant use of topical corticosteroids

	QBA4-2 (n = 352)	Pooled safety population (n = 506)
Age (years)	33.0 (11.1)	32.6 (10.8)
Sex, n (%)		
Men	223 (63.4)	318 (62.8)
Women	129 (36.6)	188 (37.2)
Duration of AD (years)	23.9 (12.2)	24.2 (11.7)
mEASI score	8.8 (4.9)	10.5 (5.6)
IGA score, n (%)		
0 (clear), 1 (almost clear)	0	2 (0.4)
2 (mild)	110 (31.3)	115 (22.7)
3 (moderate)	215 (61.1)	304 (60.1)
4 (severe)	27 (7.7)	85 (16.8)
Pruritus NRS score	4.7 (2.0)	4.8 (2.0)
Percentage of BSA affected by AD	19.6 (6.9)	21.1 (7.6)
Exposure to delgocitinib ointment		
Exposure duration (days)	286.7 (118.4)	251.3 (114.5)
Amount of drug applied (g)	1360.8 (869.7)	1238.6 (786.7)
Amount of drug applied per day (g)	4.8 (2.2)	5.1 (2.3)
Patients who used topical corticosteroids, n (%)	224 (63.6)	288 (56.9)

Data are displayed as mean (SD) unless otherwise indicated. The pooled safety population includes all patients in QBA4-2 and patients who received delgocitinib ointment in QBA4-1. AD, atopic dermatitis; BSA, body surface area; IGA, Investigator's Global Assessment; mEASI, modified Eczema Area and Severity Index; NRS, Numeric Rating Scale.

**Table 3.** Summary of adverse events

	QBA4-2 (n = 352)	Pooled safety population (n = 506)
Adverse events	271 (77.0)	349 (69.0)
Maximum severity		
Mild	218 (61.9)	286 (56.5)
Moderate	52 (14.8)	62 (12.3)
Severe	1 (0.3)	1 (0.2)
Treatment-related adverse events	69 (19.6)	78 (15.4)
Serious adverse events	7 (2.0)	7 (1.4)
Adverse events leading to discontinuation	16 (4.5)	17 (3.4)

Data are displayed as number of patients (%). The pooled safety population includes all patients in QBA4-2 and patients who received delgocitinib ointment in QBA4-1.

### Pharmacokinetics

Plasma concentrations of delgocitinib were not detected in more than 80% of patients throughout the treatment period. No apparent difference between study visits was found in the

**Table 4.** Adverse events occurring in 2% or more of patients

	QBA4-2 (n = 352)	Pooled safety analysis population (n = 506)
Eye disorders		
Allergic conjunctivitis	8 (2.3)	11 (2.2)
Gastrointestinal disorders		
Dental caries	7 (2.0)	11 (2.2)
General disorders and administration site conditions		
Application site acne	14 (4.0)	16 (3.2)
Immune system disorders		
Seasonal allergy	9 (2.6)	10 (2.0)
Infections and infestations		
Nasopharyngitis	101 (28.7)	131 (25.9)
Application site folliculitis	15 (4.3)	18 (3.6)
Influenza	17 (4.8)	17 (3.4)
Kaposi's varicelliform eruption	11 (3.1)	17 (3.4)
Herpes simplex	12 (3.4)	15 (3.0)
Folliculitis	10 (2.8)	12 (2.4)
Gastroenteritis	10 (2.8)	12 (2.4)
Paronychia	7 (2.0)	11 (2.2)
Oral herpes	10 (2.8)	10 (2.0)
Skin and subcutaneous tissue disorders		
Contact dermatitis	20 (5.7)	23 (4.5)
Acne	17 (4.8)	22 (4.3)
Eczema	9 (2.6)	10 (2.0)

Data are displayed as number of patients (%). The pooled safety population includes all patients in QBA4-2 and patients who received delgocitinib ointment in QBA4-1.

proportion of patients with detectable plasma concentrations of delgocitinib (Table S2).

### Efficacy

The proportion of patients with mEASI-50 and mEASI-75 was increased after the start of delgocitinib treatment and was maintained throughout the treatment period (Fig. 2). The proportion of patients with mEASI-50 was 31.5% (104/330) at week 4, 42.3% (121/286) at week 24 and 51.9% (136/262) at week 52. The proportion of patients with mEASI-75 was 10.9% (36/330) at week 4, 22.7% (65/286) at week 24 and 27.5% (72/262) at week 52. The improvement in the IGA and pruritus NRS scores was also noted at weeks 4, 24 and 52 (Table S3).

### DISCUSSION

Long-term treatment with delgocitinib 0.5% ointment, a novel topical JAK inhibitor, was well tolerated in Japanese patients aged 16 years or older with mild to severe AD. Safety results in the long-term studies were similar to those in the 4-week phase 2 study.<sup>18</sup> No new safety concerns emerged with delgocitinib treatment for up to 52 weeks. Most AEs were mild and unrelated to delgocitinib ointment. The incidence of AEs did not increase over time, except for seasonal diseases.

Long-term treatment with delgocitinib ointment did not cause skin atrophy or telangiectasia, as seen with topical

**Table 5.** Treatment-related adverse events occurring in 1% or more of patients

	QBA4-2 ( <i>n</i> = 352)	Pooled safety population ( <i>n</i> = 506)
Application site folliculitis	11 (3.1)	12 (2.4)
Application site acne	10 (2.8)	11 (2.2)
Application site irritation	9 (2.6)	9 (1.8)
Kaposi's varicelliform eruption	5 (1.4)	8 (1.6)
Application site erythema	7 (2.0)	7 (1.4)
Contact dermatitis	6 (1.7)	6 (1.2)

Data are displayed as number of patients (%). The pooled safety population includes all patients in QBA4-2 and patients who received delgocitinib ointment in QBA4-1.

corticosteroids.<sup>1,3</sup> Application site irritation symptoms, as commonly reported with tacrolimus ointment,<sup>1,3</sup> were infrequent and mild. Most irritation symptoms occurred in the first 2 weeks of delgocitinib treatment, the incidence of which decreased with time. Similarly, local skin infections, including application site folliculitis and Kaposi's varicelliform eruption, were infrequent; however, appropriate monitoring of local skin infections is mandatory given the immune-suppressive activity of delgocitinib. As consistent with the previous studies,<sup>18,19</sup> systemic exposure to delgocitinib was low throughout the long-term treatment, indicating that delgocitinib ointment is unlikely to cause systemic infections due to excessive immunosuppression. Overall, the safety results indicate that

delgocitinib ointment has a favorable safety profile as a topical agent for AD.

Previous studies<sup>18,19</sup> demonstrated that delgocitinib ointment rapidly improved clinical signs and symptoms, as assessed with mEASI, IGA and pruritus NRS scores, in Japanese patients aged 16 years or older with moderate to severe AD. In the present study, the improvement effects on AD were maintained with delgocitinib treatment for up to 52 weeks. Because patients were allowed to continue to use strong or less potent topical corticosteroids<sup>1</sup> (with similar potency to class III to VII [medium to lowest] corticosteroids in the USA)<sup>3</sup> and tacrolimus ointment immediately before delgocitinib treatment initiation, the efficacy results may represent a disease response to switching to delgocitinib ointment from other agents in a real clinical setting.

The results of the present phase 3 studies should not be directly compared with clinical data of other existing topical drugs for AD, such as topical corticosteroids and calcineurin inhibitors, as well as phosphodiesterase 4 inhibitors, because of different study methods and populations. The present study was conducted in an open-label manner without any control group, which might have led to assessment bias. Additionally, the present study did not include pediatric patients with a higher prevalence of AD. A phase 3 study of delgocitinib ointment is currently being conducted in Japanese pediatric patients with AD.<sup>22</sup>

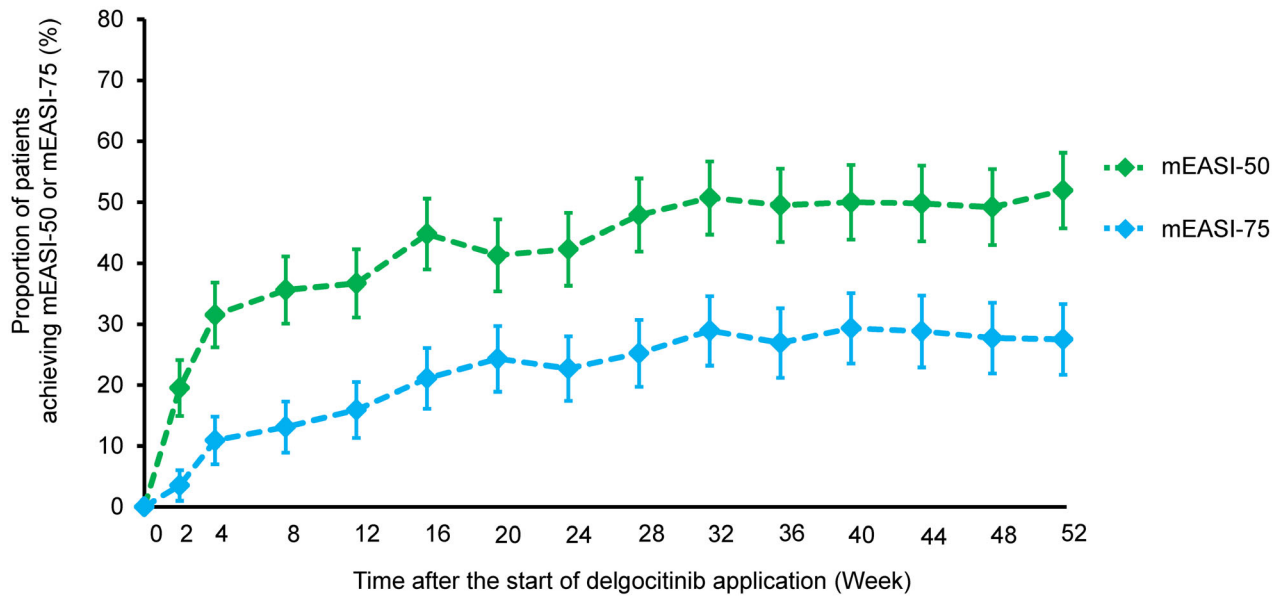
In conclusion, delgocitinib 0.5% ointment was well tolerated and effective when administrated to Japanese adult patients with AD for up to 52 weeks. Delgocitinib ointment is expected

**Table 6.** Adverse events occurring in 2% or more of patients in the pooled safety population by time period

	Onset of adverse events			
	Week 0–12 ( <i>n</i> = 506)	Week 12–24 ( <i>n</i> = 463)	Week 24–36 ( <i>n</i> = 417)	Week 36–52 ( <i>n</i> = 279)
Eye disorders				
Allergic conjunctivitis	2 (0.4)	2 (0.4)	5 (1.2)	2 (0.7)
Gastrointestinal disorders				
Dental caries	4 (0.8)	2 (0.4)	4 (1.0)	1 (0.4)
General disorders and administration site conditions				
Application site acne	10 (2.0)	3 (0.6)	2 (0.5)	4 (1.4)
Immune system disorders				
Seasonal allergy	0	0	6 (1.4)	4 (1.4)
Infections and infestations				
Application site folliculitis	6 (1.2)	6 (1.3)	2 (0.5)	5 (1.8)
Folliculitis	4 (0.8)	6 (1.3)	0	2 (0.7)
Gastroenteritis	3 (0.6)	2 (0.4)	5 (1.2)	3 (1.1)
Herpes simplex	9 (1.8)	4 (0.9)	1 (0.2)	6 (2.2)
Influenza	0	4 (0.9)	11 (2.6)	2 (0.7)
Kaposi's varicelliform eruption	10 (2.0)	2 (0.4)	5 (1.2)	3 (1.1)
Nasopharyngitis	48 (9.5)	51 (11.0)	47 (11.3)	27 (9.7)
Oral herpes	5 (1.0)	3 (0.6)	3 (0.7)	4 (1.4)
Paronychia	4 (0.8)	4 (0.9)	2 (0.5)	1 (0.4)
Skin and subcutaneous tissue disorders				
Acne	10 (2.0)	6 (1.3)	4 (1.0)	5 (1.8)
Contact dermatitis	11 (2.2)	8 (1.7)	3 (0.7)	5 (1.8)
Eczema	4 (0.8)	5 (1.1)	1 (0.2)	0

Data are displayed as number of patients (%).





No. of patients	
N	346 344 330 320 308 299 288 286 282 280 275 270 267 264 262
mEASI-50	- 67 104 114 113 134 119 121 135 142 136 135 133 130 136
mEASI-75	- 12 36 42 49 63 70 65 71 81 74 79 77 73 72

**Figure 2.** Proportion of patients achieving  $\geq 50\%$  or  $\geq 75\%$  improvement in modified Eczema Area and Severity Index (mEASI) score over time. The error bars represent two-sided 95% confidence intervals. The data from patients who used topical corticosteroids during the treatment period for the treatment of worsening of atopic dermatitis (AD) were included in the analyses. Six patients were excluded from the analyses because only the face and neck were affected by AD at baseline or the lack of baseline data on mEASI. mEASI-50,  $\geq 50\%$  improvement from baseline in the mEASI score; mEASI-75,  $\geq 75\%$  improvement from baseline in the mEASI score.

to be an alternative option with minimal safety concerns for the topical treatment of AD.

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## SUPPORTING INFORMATION

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

**Figure S1.** Study design of QBA4-1.

**Table S1.** Investigator's Global Assessment score

**Table S2.** Plasma concentrations of delgocitinib

**Table S3.** Summary of efficacy results at baseline, week 4, week 24 and week 52

**Table S4.** List of principal investigators