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RESEARCH ARTICLE

Cost-effectiveness analysis of delgocitinib in adult patients with atopic dermatitis in Japan

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Abstract

Objectives: This study evaluated the cost-effectiveness of delgocitinib relative to moisturization therapy in adult patients with moderate to severe atopic dermatitis.

Methods: The analysis was performed by using the simulation model with the patient-level data from a phase 3 study and its longterm extension study (QBA4-1 Study). The analysis was conducted from the Japanese public healthcare payer's perspective and included only direct medical costs. Health outcomes were evaluated by quality-adjusted life years. The time horizon of the analysis was one year and no discount rate was applied. In this analysis model, health states were divided into four according to the Investigator's Global Assessment score. The cost-effectiveness was determined by the incremental cost-effectiveness ratio using the willingness-to-pay threshold of 5 million JPY/quality-adjusted life years. A probabilistic sensitivity analysis was conducted to evaluate the uncertainty of each parameter used for the analysis.

Results: Total cost and quality-adjusted life years gained were 358,810 JPY and 0.867 quality-adjusted life years for delgocitinib, and 85,890 JPY and 0.798 quality-adjusted life years for moisturization therapy, respectively. The incremental cost-effectiveness ratio of delgocitinib relative to moisturization therapy was estimated to be 3.92 million JPY/quality-adjusted life years. The probability of incremental cost-effectiveness ratio of delgocitinib vs moisturization therapy being below 5 million JPY/quality adjusted life years was 79.1%.

Conclusions: Delgocitinib was rated as a cost-effective treatment relative to moisturization therapy in adults with moderate to severe atopic dermatitis. Data comparing the drug for reducing inflammation is required.

KEYWORDS
atopic, cost-benefit analysis, delgocitinib, dermatitis, quality-adjusted life years

1 | INTRODUCTION

Atopic dermatitis (AD) is a disease whose major lesion is itchy eczema which repeats cycles of aggravation and alleviation.[1] AD usually develops during infancy or early childhood and the number of AD patients decreases with age, with the disease undergoing transition to the adult type AD in a small percentage of patients. It has been reported that the AD prevalence was 10.2% at age 20-29, 8.3% at age 30-39, 4.1% at age 40-49, 2.5% at age 50-59, and 2.5% at age 60-69.[2]

The basic methods of AD treatment are (1) drug therapy, (2) skin care with topical moisturizing agents, and (3) identification of aggravating factors and countermeasures. Corresponding to the state of rash and background in individual patients, an appropriate combination of two or more methods of treatment is applied. Because no radical treatment of this disease is available, drug therapy is applied as a symptomatic therapy, as a rule, initially in the form of topical drug therapy.[1,3]

Topical steroid is used for topical drug therapy playing a central role in the treatment of AD. However, prolonged use of topical steroid can cause specific adverse reactions such as steroid-induced flushing and skin atrophy and has been reported to have the potential of causing adverse reactions similar to those seen after oral steroid treatment such as suppression of adrenal function. Because of these adverse reactions, there are many cases where patients tend to avoid the use of steroid, resulting in poor responses to the therapy. Furthermore, when steroid is used on the face or neck, the drug absorption rate is higher than that at the other sites, requiring particular attention to adverse reactions at the steroid-applied site of face/neck. It has therefore been recommended to avoid prolonged use of this kind of drug and to apply topical steroid preparations of medium or lower potency when steroid is used on the face or neck.[1,3]

Tacrolimus ointment suppresses inflammation via a mechanism different from that of topical-dose steroid and is therefore expected to manifest high efficacy even against AD for which treatment with topical steroid has been difficult due to the concern over adverse reactions. From the viewpoint of drug absorption in vivo, tacrolimus ointment has been positioned as a drug highly indicated for face and neck rash. Meanwhile, tacrolimus ointment has skin irritability (such as burning sensation) when applied to the skin and, because of safety concerns, the Use Guidance[4] strictly limits the patients and sites to whom/which the drug is applicable.[5] Thus, unlike the use of topical steroid, there are restrictions on the use of tacrolimus ointment.

Delgocitinib (Corectim® Ointment 0.5%) is the first Janus kinase (JAK: playing a significant role in intracellular signal transduction for immune activation) inhibitor for topical use developed in the world for alleviation of AD through JAK inhibition and suppression of excessive activation of immune reactions. This drug is promising as a drug possible to be used for a long period of time for remission induction therapy and remission maintenance therapy while suppressing the factors involved in the pathogenesis and progression of AD (reduction in skin barrier function, inflammation, and pruritus). The efficacy of delgocitinib has been evaluated in a phase 3 study and its long-term extension study in patients with moderate to severe AD aged 16 and over (QBA4-1 Study) and a phase 3 long-term study in patients with mild to severe AD aged 16 and over (QBA4-2 Study). In the phase 3 study (QBA4-1 Study), either delgocitinib or a placebo was applied repeatedly (twice daily) for 4 weeks at a dose level of 5 g/dose at maximum. In that study, delgocitinib was shown to be superior to the placebo in terms of the primary endpoint, that is, percent change in the modified Eczema Area and Severity Index (mEASI) score at 4 weeks after the start of treatment (−44.3% vs 1.7%, $P < .001$).[6] In the QBA4-2 Study, delgocitinib was applied repeatedly (twice daily) for 52 weeks at a dose level of 5 g/dose at maximum and has been shown to be safe when used for a long period of time.[7]

Delgocitinib is a novel topical-dose drug for the treatment of AD expected to add a new alternative to the drugs conventionally available for the treatment of AD (topical steroid and tacrolimus ointment). If these three drugs are selected appropriately and flexibly in individual cases, improvement of the quality of life (QOL) of AD patients is expected. Meanwhile, under the current tight medico-economic status of Japan where it is required to use the limited medical resources efficiently, evaluation of cost-effectiveness of a new treatment relative to the existing treatment is essential. The present study was undertaken to evaluate the cost-effectiveness of delgocitinib relative to moisturization therapy in adults with moderate to severe AD.

2 | METHODS

2.1 | Analysis outline and model structure

The cost-effectiveness analysis of delgocitinib relative to moisturization therapy was conducted by using a simulation model with the patient-level data from the QBA4-1 Study. Quality-adjusted life year (QALY) was used as an indicator of health outcomes, and the analysis was conducted from the Japanese public healthcare payer's perspective and included only direct medical costs. The time horizon of the analysis was one year. Because the analysis period was short, no discount rate was applied.[8] With reference to the previous studies of cost-effectiveness analysis related to AD,[9–11] in this analysis model, health states were divided into four (IGA0/1, IGA2, IGA3, and IGA4/5) according to the Investigator's Global Assessment (IGA) scores (an indicator of the severity of AD) (Figure 1). The patients were entered into the analysis model on the basis of their IGA scores (IGA score 3-4) at the baseline of the QBA4-1 Study, and the severity rating defined by the IGA scores was renewed at intervals of 4 weeks.

2.2 | Model parameters

2.2.1 | Transition probability

Changes over time in the IGA score-based severity of AD during delgocitinib or moisturization therapy were analyzed using the

patient-level data from the QBA4-1 Study.[6] The QBA4-1 Study consisted of a 4-week placebo-controlled double-blind randomized parallel-group study (phase 3 study) and a subsequent open-label uncontrolled study for evaluation of safety and efficacy during long-term (24-week) treatment (long-term extension study). During the long-term extension study, delgocitinib was administered also to patients who had been allocated to the placebo group during the preceding phase 3 study. However, only the data allocated to the delgocitinib group throughout the phase 3 study and the long-term extension study (28 weeks in total) was used. In the phase 3 study, concomitant use of oral-dose steroid, tacrolimus hydrate ointment, oral-dose cyclosporin, humanized anti-human interleukin (IL) −4/13 receptor monoclonal antibody, and phototherapy was prohibited, and concomitant use of topical steroid was also prohibited as a rule. There is no restriction about the use of moisturizer, however, heparin analogue, white vaseline and/or zinc oxide (in descending order) were commonly used as prescribing drugs in this study. We therefore considered it possible to use the data from the placebo group of the phase 3 study in evaluation of the efficacy of moisturization therapy. The data from the patients allocated to the placebo group in the phase 3 study (data covering 4 weeks in total) were adopted for evaluation of the efficacy of moisturization therapy. During the first 28 week of the cost-effectiveness analysis, changes over time (every 4th week) in the IGA score-based severity of delgocitinib in the QBA4-1 study was set. The percentage of each severity after 28 weeks was assumed to remain at 28 weeks. Changes over time in the IGA score-based severity of the moisturization therapy group were set based on the IGA score at each evaluation point in the placebo group of the phase 3 study during the first 4 weeks of analysis. Because placebo treatment was limited to the 4-week period, we assumed that the severity at Week 4 would remain unchanged thereafter in the placebo group. The Last Observation Carried Forward (LOCF) method was applied to the dropout cases and cases with missing IGA scores (Figure 2).

During the phase 3 study, 106 subjects received delgocitinib and 52 subjects received a placebo. The background variables of the patients enrolled to the QBA4-1 Study are shown in Table 1. There was no major discrepancy in the background variables between the two groups of the phase 3 study. The percentage of patients rated at each severity category on the basis of IGA scores at each point of evaluation is shown in Table 2.

2.2.2 | Cost

The drug cost of delgocitinib was calculated using the actual dose data recorded in the case report form of the QBA4-1 Study. The drug quantity administered per patient was calculated as 155.61 g/4 weeks, thus the drug cost for delgocitinib per 4 weeks was calculated to be 21,739 JPY (Corectim® 0.5% Ointment, 139.70 JPY/g) (Table 3).

The treatment costs related to AD other than the drug cost for delgocitinib were set for each IGA category and were assumed to be equal to those for moisturization therapy. A previous study estimating the costs for treatment of each severity class of AD among Japanese patients[12] was used for calculation of these costs. In that study, a web survey of 100 Japanese dermatologists was conducted to investigate the medical resources usage for AD treatment, and the treatment costs for AD patients were estimated for each severity class. From the costs estimated in that study, the costs for the above-mentioned prohibited concomitant therapies were deducted

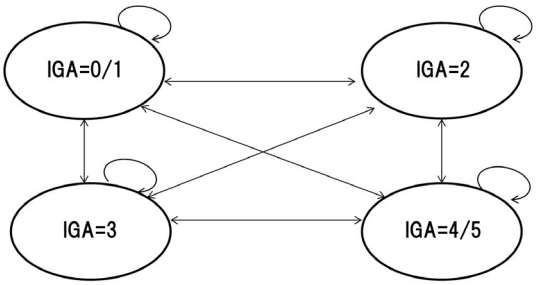

FIGURE 1 Structure of the analysis model

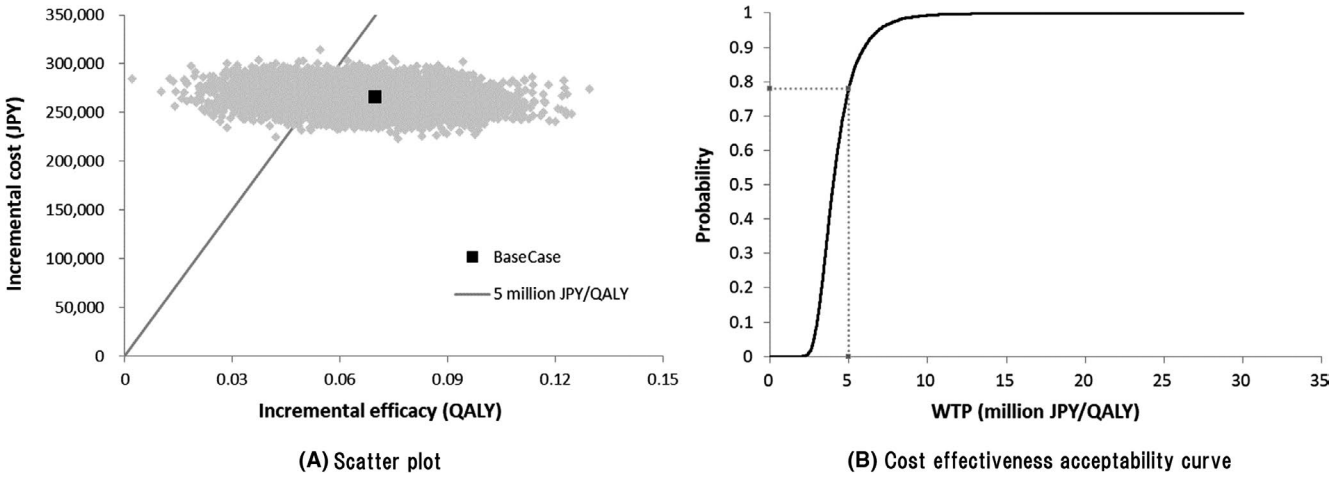

FIGURE 2 Results of the probabilistic sensitivity analysis

TABLE 1 Patients characteristics in QBA4-1 study

Variable (unit)	Moisturization therapy (N = 52)	Delgocitinib (N = 106)
Age (years)	32.3 ± 11.2	31.4 ± 9.6
Gender (male %)	34 (65.4%)	64 (60.4%)
Height (cm)	164.80 ± 7.42	164.44 ± 8.73
Body weight (kg)	63.47 ± 11.02	62.29 ± 11.83
BMI (kg/m^2)	23.30 ± 3.19	22.94 ± 3.47
Duration of atopic dermatitis (years)	24.8 ± 11.1	24.7 ± 9.7
IGA score	3.3 ± 0.5	3.3 ± 0.5
mEASI	14.539 ± 3.753	14.173 ± 3.518
TARC (pg/ml)	1224.1 ± 1249.5	1387.5 ± 1678.0
Serum total IgE (IU/ml)	3269.5 ± 5151.3	4012.7 ± 5165.9
Prior treatment (present, %)	48 (92.3%)	96 (90.6%)
Details of prior treatment (some duplications (%) = relative to all prior treatment present cases)		
Oral steroid	1 (2.1%)	2 (2.1%)
Cyclosporin	0	1 (1.0%)
Topical steroid	46 (95.8%)	93 (96.9%)
Strongest	6 (12.5%)	12 (12.5%)
Very strong	29 (60.4%)	57 (59.4%)
Strong	22 (45.8%)	41 (42.7%)
Medium	21 (43.8%)	58 (60.4%)
Weak	1 (2.1%)	0
Tacrolimus hydrate ointment	13 (27.1%)	23 (24.0%)
Other drugs	2 (4.2%)	5 (5.2%)
Other therapies	3 (6.3%)	6 (6.3%)
Information on dropout from confirmatory study		
Dropout from confirmatory study	23 (44.2%)	8 (7.6%)
Transition to Part 2 (due to aggravation)	20	8
Disease progression	2	0
Consent canceled by patient	1	0
Participation in long-term extension study	48 (92.3%)	106 (100.0%)

Note: Mean ± SD.

Abbreviations: BMI, Body Mass Index; IgE, Immunoglobulin E; IU, International Unit; TARC, Thymus and activation-regulated chemokine.

for use in the current analysis. Table 3 listed the cost parameters employed in the current analysis.

2.2.3 | Utilities

As health utilities had not been measured in the QBA4-1 Study, the numeric rating scale (NRS) data on pruritus collected in the QBA4-1 Study was converted into utilities, using the equation for utility prediction reported by Park et al.[13] Park et al conducted measurement with EuroQOL 5 dimensions 3-level (EQ-5D-3L) and Visual Analogue Scale (VAS) for pruritus in Korea (n = 268) and the following prediction equation consisting of the pruritus VAS, gender, and age was constructed;

$$\text{Utility (EQ - 5D - 3L based)} = 1.37778 - 0.00807 \times \text{pruritus VAS score} - 0.01082 \times \text{age} + 0.00013 \times \text{age}^2 + 0.00145 \times \text{gender}$$

(gender: a dummy variable, allocating 1 to female)

Because the pruritus VAS is a 0-100 scale while the pruritus NRS is a 0-10 scale, the score for the pruritus NRS was multiplied by 10 before being applied to the above-given prediction equation.

Regarding the utility converted with the prediction equation, the cost-effectiveness analysis was conducted under two settings: (1) analysis of using the health state utility of each IGA category, and (2) analysis of changes over time in the utility in each treatment group. The setting (1) was used for base-case analysis and the setting (2) for scenario analysis.

TABLE 2 Transition probabilities

Item		IGA score				Setting for probabilistic sensitivity analysis	
		0/1	2	3	4/5	Analytical method	Source
Delgocitinib	Baseline	NA	NA	68.87%	31.13%	Bootstrap	QBA4-1 Study
	4 weeks	10.38%	36.79%	39.62%	13.21%		
	8 weeks	11.32%	31.13%	41.51%	16.04%		
	12 weeks	14.15%	33.96%	43.4%	8.49%		
	16 weeks	14.15%	33.02%	44.34%	8.49%		
	20 weeks	13.21%	35.85%	44.34%	6.6%		
	24 weeks	14.15%	32.08%	48.11%	5.66%		
	28 weeks and afterward[a]	18.87%	31.13%	41.51%	8.49%		
Moisturization therapy	Baseline	NA	NA	69.23%	30.77%		
	4 weeks and afterward[a]	3.85%	9.62%	48.08%	38.46%		

Abbreviation: NA, not applicable.

[a] In the moisturization therapy group, the state at Week 4 was assumed to continue from Week 8 on. In the delgocitinib group, the state at the final evaluation was assumed to continue after the end of the study period.

Health state utility of each IGA category

The utility corresponding to a given IGA category was estimated from the IGA score at Week 4 of the phase 3 study, and the utility for each health state calculated with the prediction equation. The utility for each IGA category was estimated with a linear model in which the utility served as a dependent variable, the IGA score served as an independent variable and the gender and age treated as covariables. The estimated utility for each IGA category is shown in Table 4.

Changes over time in the utility following each therapy

Changes over time in the utility following each therapy were analyzed using the data on each evaluation points of the phase 3 study and its long-term extension study.

Estimation of the change in utility at each point of time was conducted with a linear mixed effect model in which the utilities served as a dependent variable, the treatment group, point of time (Week 1, 2, 3, and 4), the treatment group x point of time, gender, age, baseline utility, and baseline IGA score served as the fixed effect and the

TABLE 3 Cost parameters

Item		Value	Setting for probabilistic sensitivity analysis			Source
			Analytical method	Distribution	α, β	
Delgocitinib NHI price (\/g)		139.7	-	-	-	Corectim®0.5% Ointment NHI price
Delgocitinib quantity used in 4 weeks (g)		155.61	Bootstrap	-	-	QBA4-1 Study
Treatment cost for each IGA score (\/4 weeks)	0/1	5358	Monte Carlo simulation	Gamma distribution	100, 53.583	Murota et al
	2	5358	Monte Carlo simulation	Gamma distribution	100, 53.583	
	3	5844	Monte Carlo simulation	Gamma distribution	100, 58.436	
	4/5	8017	Monte Carlo simulation	Gamma distribution	100, 80.172	

Note: The same cost was used because the treatment rated at score 0/1 is assumed to be similar to the treatment rated at score 2.
Abbreviation: NHI, National Health Insurance.

TABLE 4 Utility for each IGA score (base-case analysis)

Item		Value	95%CI	Setting for probabilistic sensitivity analysis			Source
				Analytical method	Distribution	α, β	
IGA score	0/1	0.952	0.879-1.025	Monte Carlo simulation	Beta distribution	3.672, 0.184	QBA4-1 Study, Park, et al
	2	0.939	0.898-0.980	Monte Carlo simulation	Beta distribution	3.437, 0.446	
	3	0.830	0.798-0.863	Monte Carlo simulation	Beta distribution	3.891, 0.861	
	4/5	0.707	0.662-0.753	Monte Carlo simulation	Beta distribution	4.843, 2.173	

Abbreviation: CI, Confidence Interval.

TABLE 5 Utility at each time point (scenario analysis)

Item		Value	95%CI	Source
Delgocitinib	Baseline	0.770	-	QBA4-1 Study, Park, et al
	4 weeks	0.874	0.852-0.896	
	8 weeks	0.822	0.786-0.858	
	12 weeks	0.842	0.806-0.878	
	16 weeks	0.840	0.802-0.877	
	20 weeks	0.842	0.806-0.879	
	24 weeks	0.839	0.801-0.877	
	28 weeks and afterward[a]	0.857	0.817-0.896	
Moisturization therapy	Baseline	0.771	-	
	4 weeks and afterward[a]	0.784	0.753-0.814	

Abbreviation: CI, Confidence Interval.
[a] In the moisturization therapy group, the state at Week 4 was assumed to continue from Week 8 on. In the delgocitinib group, the state at the final evaluation was assumed to continue after the end of the study period.

TABLE 6 Results of analysis

	Total cost (¥)	Incremental cost (¥)	Total QALY	Incremental QALY	ICER (¥/QALY)
Base-case analysis (utility for each IGA score)					
Delgocitinib	358,810	272,920	0.867	0.070	3,923,633
Moisturization therapy	85,890	-	0.798	-	-
Scenario analysis (utility at each point of time in each therapy group)					
Delgocitinib	358,810	272,920	0.844	0.061	4,467,282
Moisturization therapy	85,890	-	0.783	-	-

study center served as the variable effect. Because the long-term extension study pertained only to the delgocitinib group, estimation of the change in utility at each point of time using the data from that study was conducted with a linear mixed effect model in which the utility served as a dependent variable, the point of time (Week 8, 12, 16, 20, 24, and 28), gender, age, baseline utility, and baseline IGA score as the fixed effect and the study center served as the variable effect. Missing data about utility at any point of time was replenished by the LOCF method.

The estimated changes over time in utility after the start of each therapy are shown in Table 5. The subsequent course of utility shown in the table is based on the assumption that the utility at Week 4 and the utility at Week 28 continued until the end of the analysis in the moisturization therapy group and the delgocitinib therapy group, respectively.

2.3 | Conditions for analysis

The cost-effectiveness of delgocitinib was evaluated using the incremental cost-effectiveness ratio (ICER) calculated by dividing the incremental cost relative to the moisturization therapy by the incremental QALY. The threshold of ICER in this analysis was set at 5 million JPY/QALY.[14,15] Cases where the ICER was lower than 5 million JPY/QALY were rated as cost-effective.

The analyses were conducted for one-year time horizon, including a base-case analysis on the health state utility for each IGA category and a scenario analysis on changes over time in utility after the start of each therapy.

To evaluate the uncertainty of each parameter used for analysis, probabilistic sensitivity analysis (PSA) by the bootstrap method and the Monte Carlo simulation method was conducted on the base-case analysis. Regarding the changes over time in IGA score and the quantity of delgocitinib administered, resampling (106 samples and 52 samples per set, respectively) from the QBA4-1 Study was conducted, and the transition probability and the quantity administered in 4 weeks were estimated for each bootstrap sample set. Regarding the utility and the costs for each IGA category, we set random numbers followed the probability distribution set from the standard error for each parameter, and the ICER was calculated from the costs and QALY for both groups. This sequence of steps was repeated 10,000 times (Appendix 1).

3 | RESULTS

In the base-case analysis of using health state utility for each IGA category, total cost and QALY gained were 358,810 JPY and 0.867 QALY for delgocitinib, and 85,890 JPY and 0.798 QALY for moisturization therapy, respectively. On the basis of these results, the ICER of delgocitinib relative to moisturization therapy was estimated to be 3.92 million JPY/QALY (Table 6).

In the scenario analysis of changes over time in utility after the start of each therapy, total QALY gained were 0.844 QALY for delgocitinib and 0.783 QALY for moisturization therapy, respectively, thus the ICER was estimated as 4.47 million JPY/QALY (Table 6).

As a result of PSA, the probability for the ICER of delgocitinib to be equal to or lower than 5 million JPY/QALY was 79.1%. The scatter plot and the cost-effectiveness acceptability curve are given in Appendix 1.

4 | DISCUSSION

In this study, the cost-effectiveness of delgocitinib relative to moisturization therapy in adults with moderate to severe AD was evaluated with a simulation model, using the individual patient data from QBA4-1 Study. In the base-case analysis, the ICER of delgocitinib therapy relative to moisturization therapy was 3.92 million JPY/QALY, assessed as delgocitinib was cost-effective in comparison to moisturization therapy. Also in the scenario analysis, the ICER of delgocitinib relative to moisturization therapy was lower than 5 million JPY/QALY, and the probability for the ICER of delgocitinib to be lower than the threshold (5 million JPY/QALY) was as high as 79.1% in the PSA, both endorsing the results of the base-case analysis.

Although the percent change in mEASI score at Week 4 of treatment was adopted as a primary endpoint in the phase 3 study (QBA4-1 Study), the current analysis was based on the severity of the IGA score, with reference to the previously reported attempts of cost-effectiveness analysis related to AD.[9–11] The EASI scoring system is known well in Japan and abroad as an indicator for evaluation of the severity of AD on the basis of the physician's rating of the intensity and coverage of skin symptoms (erythema, invasion/papule, scratch, lichenification) at each site.[16] Because application of delgocitinib (available as ointment) to the scalp (hair-covered in most part) is restricted, the mEASI score excluding the head/neck score from the EASI score

was adopted in the QBA4-1 Study. Meanwhile, the IGA score is based on overall evaluation of the severity of skin symptoms by the physician. In the QBA4-1 Study, the percentage of subjects rated as IGA score 0 or 1 at the end of treatment was higher in the delgocitinib group (10.4%) than in the placebo group (3.8%) although the difference was not statistically significant6. IGA score is considered to resemble mEASI in terms of the evaluation method, and the model used in the current analysis seems to be capable of reflecting the superiority of delgocitinib over the placebo in terms of efficacy as shown in the QBA4-1 Study.

The present analysis, conducted using the data from the individual patient report forms of the QBA4-1 Study, involves the following limitations.

First, the utility was estimated with the use of pruritus NRS. Although AD is known to have a large impact on the QOL of patients through its symptoms rash and pruritus, the utility used in the present analysis was converted from the pruritus score alone and hence did not sufficiently reflect the total impact of the disease (including the impact of rash) on the patient's QOL. Skindex-16 (a skin disease-specific scale for evaluation of QOL) was measured also in the QBA4-1 Study, but no report was available about how to estimate the utility from the Skindex-16 score. For this reason, the pruritus VAS score was converted into utility in the present analysis. Considering that the least square average of the change in total Skindex-16 score improved significantly in the delgocitinib group compared to the placebo group in the phase 3 study (QBA4-1 Study) (placebo group: 6.49, delgocitinib group: −18.22, $P < .0001$),[6] we cannot rule out that the rash-alleviating effect of delgocitinib was underestimated in the present analysis.

The second limitation pertains to the fact that the efficacy of moisturization therapy was estimated on the basis of the data from the first 4 weeks of the phase 3 study (QBA4-1 Study). Because comparison with the placebo during the QBA4-1 Study was limited for 4 weeks, the present analysis assumed that the efficacy recorded at Week 4 would continue until one year after the start of treatment. Because moisturization therapy cannot be expected to manifest anti-inflammatory effects, the condition in the placebo group recorded at Week 4 is unlikely to improve thereafter and is rather likely to aggravate due to relapse. So, under the setting adopted for the present analysis, the efficacy of delgocitinib relative to moisturization therapy may have been evaluated conservatively.

5 | CONCLUSION

In this study, delgocitinib therapy was evaluated as cost-effective comparing to moisturization therapy in adult patients with moderate to severe AD, using the data from individual patient report forms of the QBA4-1 Study. Although there were several limitations, each limitation worked in the direction of conservative evaluation of the efficacy of delgocitinib. Cost-effectiveness evaluation comparing drugs for reducing inflammation is required in the future.

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CONFLICT OF INTEREST

H. M. received consulting fees and/or speaker honoraria from Japan Tobacco, Maruho, Shiseido, Kaken Pharmaceutical, Sanofi Genzyme, Mitsubishi Tanabe Pharma, Kyowa Kirin, Torii Pharmaceutical, Lily, Abbie, Taiho Pharma, Bristol-Myers Squibb, Kao, Novartis, Kracie, NAOS, Sato Pharmaceutical, Tokiwa Pharmaceutical, Sumitomo Dainippon Pharma, Nippon Zoki Pharmaceutical, Pola Pharma, Bayer and Teikoku Seiyaku. S. I. and H. S. are employees of CRECON Medical Assessment. CRECON Medical Assessment was paid from Japan Tobacco and Torii Pharmaceutical to conduct analyses for the study. K. Y., S. T., and A. I. are employees of Japan Tobacco. MT and MM declare no conflict of interest.

DECLARATION SECTION

Approval of the research protocol: Yes.

Informed Consent: Written informed consent was obtained from the patients.

Registry and the Registration No. of the study/trial: JapicCTI-173554.

Animal Studies: N/A.

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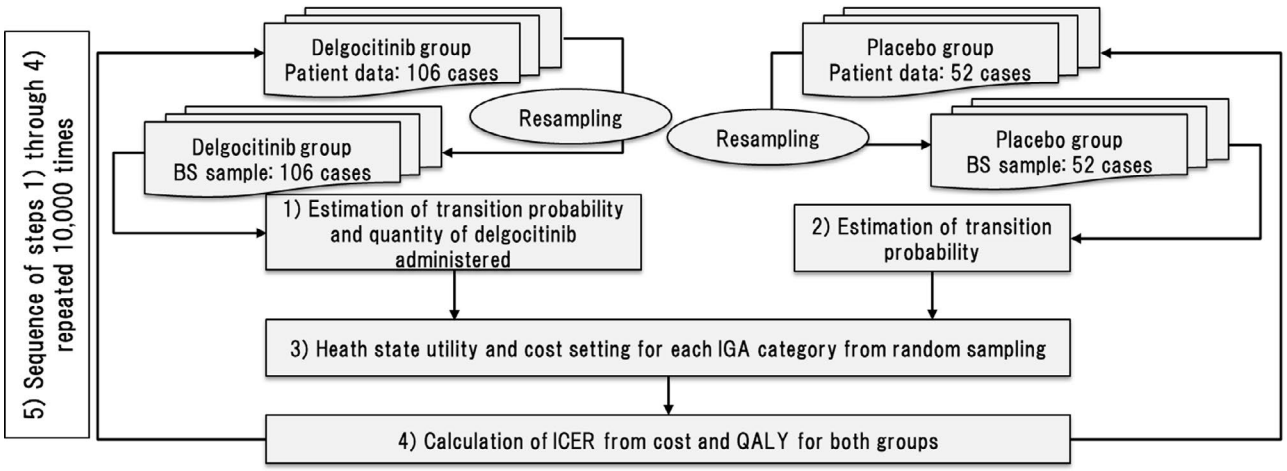
APPENDIX 1



① Resampling, permitting duplications, is conducted using the patient data from the delgocitinib group (sample size 106), followed by estimation of the transition probability and the quantity of delgocitinib administered from the bootstrap sample (Bootstrap method)
② Resampling, permitting duplications, is conducted using the patient data from the placebo group (sample size 52), followed by estimation of the transition probability in the moisturization therapy group from the bootstrap sample (Bootstrap method)
③ Heath state utility and cost setting for each IGA category from random sampling (Monte Carlo simulation)
④ Calculation of costs and QALY for both treatment, followed by calculation of ICER
⑤ The sequence of steps 1) through 4) is repeated 10,000 times, to yield 10,000 estimates (ICER).

Conceptual diagram for the probabilistic sensitivity analysis. BS, bootstrap; ICER, incremental cost effectiveness ration; QALY, quality-adjusted life year; WTP, willingness to pay