Report on the Deliberation Results

December 9, 2020

Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Olumiant Tablets 2 mg Olumiant Tablets 4 mg
Non-proprietary Name	Baricitinib (JAN*)
Applicant	Eli Lilly Japan K.K.
Date of Application	January 29, 2020

Results of Deliberation

In its meeting held on December 4, 2020, the Second Committee on New Drugs concluded that the partial change application for the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period for the present application is the remainder of the re-examination period for the initial approval of the product (until July 2, 2025).

Approval Conditions

The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

Review Report

November 25, 2020
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Olumiant Tablets 2 mg Olumiant Tablets 4 mg
Non-proprietary Name	Baricitinib
Applicant	Eli Lilly Japan K.K.
Date of Application	January 29, 2020
Dosage Form/Strength	Each tablet contains 2 or 4 mg of baricitinib
Application Classification	Prescription drug, (4) Drug with a new indication
Items Warranting Special Mention	None
Reviewing Office	Office of New Drug IV

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of atopic dermatitis in patients who have had an inadequate response to conventional treatments, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions. The safety and efficacy of the product in clinical use should be further evaluated in post-marketing surveillance.

Indications

The following diseases in patients who have had an inadequate response to conventional treatments:

Rheumatoid arthritis ~~in patients who have had an inadequate response to conventional treatments~~ (including the prevention of structural joint damage)

Atopic dermatitis

(Underline denotes additions. Strikethrough denotes deletions.)

Dosage and Administration

The usual adult dosage is 4 mg of baricitinib administered orally once daily. The dose should be reduced to 2 mg according to the patient's condition.

(No change)

Approval Conditions

The applicant is required to develop and appropriately implement a risk management plan.

Attachment

Review Report (1)

November 11, 2020

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval	
Brand Name	Olumiant Tablets 2 mg Olumiant Tablets 4 mg
Non-proprietary Name	Baricitinib
Applicant	Eli Lilly Japan K.K.
Date of Application	January 29, 2020
Dosage Form/Strength	Each tablet contains 2 or 4 mg of baricitinib
Proposed Indications	Rheumatoid arthritis in patients who have had an inadequate response to conventional treatments (including the prevention of structural joint damage) <u>Moderate to severe atopic dermatitis</u> (Underline denotes additions.)
Proposed Dosage and Administration	The usual adult dosage is 4 mg of baricitinib administered orally once daily. The dose should be reduced to 2 mg according to the patient's condition. (No change)

Table of Contents

List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Baricitinib, the active ingredient of Olumiant Tablets 2 mg and Olumiant Tablets 4 mg, is a Janus kinase (JAK) inhibitor developed by Incyte Corporation (the US). Baricitinib was approved in Japan in July 2017 for the treatment of rheumatoid arthritis in patients who have had an inadequate response to conventional treatments (including prevention of structural damage).

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by pruritic eczematous lesions. AD typically has a remitting and relapsing course. The treatment of AD varies, depending on the symptoms and characteristics of individual patients. The mainstay of treatment is a combination of the following: pharmacotherapy; topical therapy and skin care for physiological abnormalities of the skin (i.e., emollients, bathing/showering); and identification and control of risk factors for AD exacerbation (Clinical Practice Guidelines for the Management of Atopic Dermatitis 2018 [in Japanese]. the *Japanese Journal of Dermatology*. 2018;128:2431-2502). Currently recommended pharmacotherapies include topical anti-inflammatory drugs, such as topical corticosteroids (TCS) and a topical calcineurin inhibitor (TCI), tacrolimus, in combination with the regular use of emollients. The use of oral antihistamines is also recommended as an adjuvant therapy. Intermittent oral ciclosporin or subcutaneous dupilumab may be used in patients who have had an inadequate response to these therapies. The use of oral corticosteroids may be considered for induction of remission in AD patients with acute exacerbation or severe or the most severe conditions.

Baricitinib blocks the JAK signal transducer and activator of transcription (STAT) pathway, which is one of the major signaling pathways of cytokines involved in the pathogenesis of AD, such as thymic stromal lymphopoietin, interleukin (IL)-4, IL-5, IL-13, IL-22, and IL-31 (*J Allergy Clin Immnol.* 2017;139:S65-S76). Thus, the development of baricitinib was initiated with an expectation that baricitinib would be effective in the treatment of AD.

The clinical development of baricitinib for AD started in February 2016. The applicant filed a partial change application based on the results of the global clinical studies in countries including Japan. In Europe, baricitinib was approved in October 2020 for the treatment of AD. As of November 2020, baricitinib is under review in [redacted], [redacted], and other countries.

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

Since the present application is intended for the addition of a new indication, no data relating to quality were submitted.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

The present application is intended for the addition of a new indication, and non-clinical pharmacology data have already been evaluated at the approval of the initial application; therefore, no new data were submitted.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

Since the present application is intended for the addition of a new indication, no data relating to non-clinical pharmacokinetics were submitted.

5. Toxicity and Outline of the Review Conducted by PMDA

Since the present application is intended for the addition of a new indication, no data relating to toxicity were submitted.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

The concentrations of baricitinib in plasma were measured by liquid chromatography with tandem mass spectrometry (LC-MS/MS) with a quantitation range of 0.2 to 200 ng/mL.

6.2 Clinical pharmacology

The evaluation data submitted included the results from the population pharmacokinetic analyses. Unless otherwise stated, the dose of Olumiant is expressed as the dose of baricitinib.

6.2.1 Population pharmacokinetic analyses (CTD 5.3.3.5.1)

Population pharmacokinetic analyses were performed (NONMEM version 7.4.2) using plasma baricitinib concentration data (4,122 plasma concentrations measured in 819 subjects) from the following studies in patients with AD: Study I4V-MC-JAHG [see Section 7.1.1], the BREEZE-AD1 study [see Section 7.2.1], and the BREEZE-AD2 study [see Section 7.2.2].

The base model was a two-compartment pharmacokinetic model with zero-order absorption and first-order elimination processes with lag time, which included the effect of estimated glomerular filtration rate (eGFR) on apparent renal clearance (CL_r/F). Based on the results of covariate screening,[1)] the model developed by incorporating body weight as a covariate for apparent central volume of distribution (V_1/F)[2)] was selected as the final model. Table 1 shows the effect of renal impairment on the pharmacokinetics of baricitinib estimated from the final model. Using data from the 3 clinical studies shown above, $AUC_{\tau,ss}$ and $C_{max,ss}$ were estimated by the dose of baricitinib and by the severity of renal impairment of the patient (Figure 1). According to the applicant, while dose adjustment of baricitinib is not necessary in patients with mild renal impairment, a regimen of 2 mg once daily is recommended for patients with moderate renal impairment.

[1)] The following covariates were tested: baseline age, body weight, body mass index (BMI), sex, ethnicity, and treatment duration for CL_r/F and V_1/F; baseline age, body weight, BMI, and sex for apparent non-renal clearance (CL_{nr}/F).

[2)] The mean of the factors selected as covariates and their range were as follows: body weight, 74.5 [42.9, 151] kg; baseline eGFR, 107 [46.2, 154] mL/min/1.73 m^2.

Table 1. Effect of renal impairment on the pharmacokinetics of baricitinib

Severity of renal impairment	eGFR (mL/min/1.73 m^2)	Mean ratio of pharmacokinetic parameter and [90% CI] (renal impairment/normal renal function)	
		$AUC_{\tau,ss}$	$C_{max,ss}$
Mild	≥60 and <90	1.29 [1.08, 1.65]	1.07 [1.02, 1.13]
Moderate	≥30 and <60	1.61 [1.37, 2.01]	1.16 [1.11, 1.22]

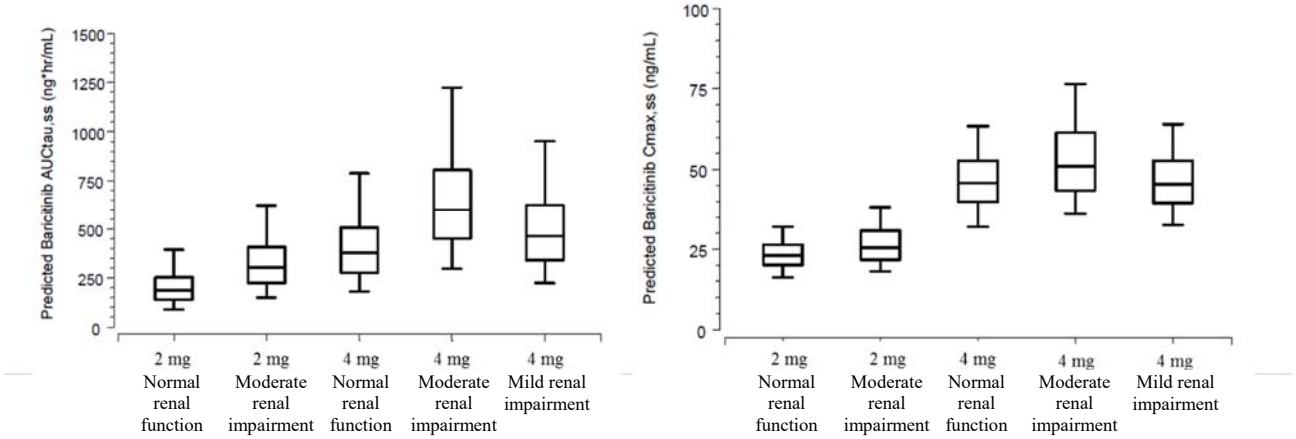

Figure 1. The pharmacokinetic parameters of baricitinib by baricitinib dose and severity of the patient's renal impairment estimated from the population pharmacokinetic model
Lower box edge, 25th percentile; middle line, 50th percentile; upper box edge, 75th percentile
Lower whisker, 5th percentile; upper whisker, 95th percentile

6.R Outline of the review conducted by PMDA

The applicant's explanation about ethnic differences in the pharmacokinetics of baricitinib between Japanese and non-Japanese patients with AD, as well as differences in the pharmacokinetics between patients with AD and patients with RA:

- Ethnic differences in pharmacokinetics of baricitinib between Japanese and non-Japanese patients with AD

Figure 2 shows plots of plasma baricitinib concentration versus time data (measured data) used for population pharmacokinetic analyses [see Section 6.2.1]. At all dose levels, the data set of Japanese patients with AD overlaps considerably with that of non-Japanese patients with AD, indicating that there were no significant differences in scattering between the populations. As shown in Table 2, the pharmacokinetic parameters of baricitinib estimated retrospectively from the population pharmacokinetic model were similar in Japanese and non-Japanese patients with AD.

Based on the above, there have been no clear ethnic differences in the pharmacokinetics of baricitinib in patients with AD.

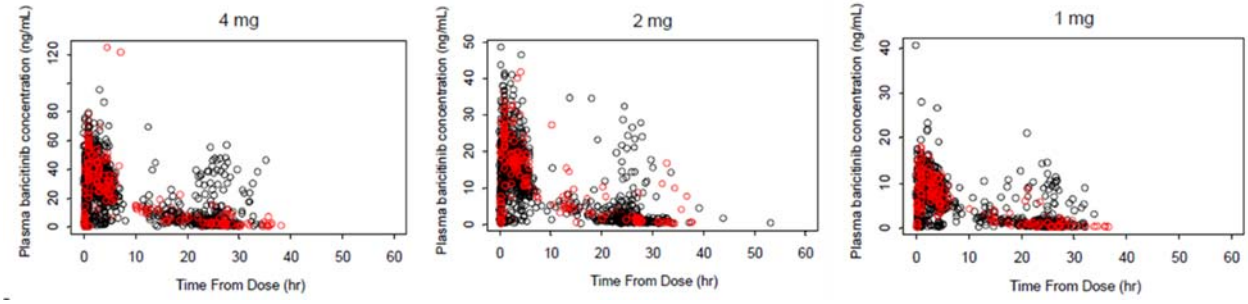

Figure 2. Plots of plasma baricitinib concentration versus time data following administration of baricitinib 1, 2, or 4 mg once daily to Japanese and non-Japanese patients with AD (measured data)
Black circles, non-Japanese patient's data; red circles, Japanese patient's data

Table 2. Pharmacokinetic parameters of baricitinib in Japanese and non-Japanese patients with AD estimated retrospectively using the population pharmacokinetic model

Population	Dosage regimen	$AUC_{\tau,ss}$ (ng·h/mL)	$C_{max,ss}$ (ng/mL)
Japanese	4 mg once daily	387 (37)	47.8 (16)
Non-Japanese		422 (52)	45.5 (22)

Mean (coefficient of variation [CV]%)

- Difference in pharmacokinetics of baricitinib between patients with AD and those with RA

The mean of pharmacokinetic parameters at steady state following administration of baricitinib 4 mg once daily to patients with AD estimated using the population pharmacokinetic model was 415 ng·h/mL (CV = 50%) for $AUC_{\tau,ss}$ and 45.9 ng/mL (CV = 21%) for $C_{max,ss}$. The estimated baricitinib exposure at steady state following administration of baricitinib 4 mg once daily to patients with RA was 478 ng·h/mL (CV = 40.7%) for $AUC_{\tau,ss}$ and 53.4 ng/mL (CV = 21.8%) for $C_{max,ss}$ [see Review Report of "Olumiant Tablets 2 mg and Olumient Tablets 4 mg" dated May 19, 2017]. The above results suggest no clear differences in the pharmacokinetics of baricitinib between patients with AD and those with RA.

PMDA's view:

The applicant's explanation was accepted. There is no particular problem, in terms of pharmacokinetics, with evaluating the efficacy and safety of baricitinib on the basis of data from the global clinical studies that enrolled participants from Japan.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted the main efficacy and safety data in the form of results from 6 studies summarized in Table 3.

Table 3. Main data submitted

Data category	Phase	Study ID	Location	Study population	N of subjects	Summary of dosage regimen (oral administration in all regimens)	Main endpoints
Evaluation	II	I4V-MC-JAHG	Global	Patients with AD and a history of inadequate response to conventional treatments (e.g., TCS, OCS, antibiotics, and immune modulators)	(1) 37 (2) 38 (3) 49	(1) Baricitinib 2 mg QD (2) Baricitinib 4 mg QD (3) Placebo QD	Efficacy Safety
Evaluation	III	BREEZE-AD1 (I4V-MC-JAHL)	Global	Patients with AD who have a history of inadequate response to TCS of at least moderate potency or in whom TCS is not recommended because of safety reasons	(1) 127 (2) 123 (3) 125 (4) 249	(1) Baricitinib 1 mg QD (2) Baricitinib 2 mg QD (3) Baricitinib 4 mg QD (4) Placebo QD	Efficacy Safety
Evaluation	III	BREEZE-AD2 (I4V-MC-JAHM)	Global	Patients with AD who have a history of inadequate response to TCS of at least moderate potency or in whom TCS is not recommended because of safety reasons	(1) 125 (2) 123 (3) 123 (4) 244	(1) Baricitinib 1 mg QD (2) Baricitinib 2 mg QD (3) Baricitinib 4 mg QD (4) Placebo QD	Efficacy Safety
Evaluation	III	BREEZE-AD7 (I4V-MC-JAIY)	Global	Patients with AD who have a history of inadequate response to TCS of at least moderate potency	(1) 109 (2) 111 (3) 109	(1) Baricitinib 2 mg QD (2) Baricitinib 4 mg QD (3) Placebo QD	Efficacy Safety
Reference	III	BREEZE-AD4 (I4V-MC-JAIN)	Global	Patients with AD who have a history of inadequate response to TCS of at least moderate potency and have a history of inadequate response to ciclosporin, or who are intolerant to or have a contraindication to, ciclosporin	(1) 93 (2) 185 (3) 92 (4) 93	(1) Baricitinib 1 mg QD (2) Baricitinib 2 mg QD (3) Baricitinib 4 mg QD (4) Placebo QD	Efficacy Safety
Evaluation	III	BREEZE-AD3 (I4V-MC-JAHN)	Global	A: Patients with AD who completed BREEZE-AD1, BREEZE-AD2, or BREEZE-AD7 Dosage regimens (1), (2), (3), and (4) B: Patients with AD who had not participated in any of the above 3 studies and had an inadequate response to TCS of at least moderate potency or in whom TCS is not recommended because of safety reasons Dosage regimen (5) (a cohort added)	(1) 45 (2) 512 (3) 730 (4) 86 (5) 247	(1) Baricitinib 1 mg QD (2) Baricitinib 2 mg QD (3) Baricitinib 4 mg QD (4) Placebo QD (5) Baricitinib 2 mg QD	Efficacy Safety

Moderate potency = a class having potency that is equivalent to the medium to strong class in Japan's classification system

7.1 Phase II study

7.1.1 Global clinical study in patients with moderate to severe AD (TCS combination study, CTD 5.3.5.1.1, Study I4V-MC-JAHG [February 2016 to March 2017])

A randomized, double-blind, placebo-controlled, parallel-group study was conducted in Japan and the US to evaluate the efficacy and safety of baricitinib in combination with TCS in patients with moderate to severe AD and a history of inadequate response to conventional treatments[3)] (target sample size, 120 subjects [36 subjects each in the 2 mg and 4 mg groups and 48 subjects in the placebo group]).

Subjects were to receive placebo or baricitinib 2 mg or 4 mg once daily orally for 16 weeks. Subjects had to use triamcinolone 0.1% cream (classified as medium potency TCS in Japan) in the 4 weeks prior to randomization (baseline) and continue the use of the TCS throughout the study.

A total of 124 subjects were randomized with country as a stratification factor (37 subjects in the 2 mg group, 38 subjects in the 4 mg group, and 49 subjects in the placebo group) and were included in the intent-to-treat (ITT) population. The efficacy analysis population was the ITT population. Of the randomized subjects, those who received at least 1 dose of the study drug were included in the safety analysis set. The safety analysis set was consequently the same as the ITT population in this study.

[3)] Eligible patients were patients with AD aged ≥18 years who met all the inclusion criteria. Key inclusion criteria: (1) having a diagnosis of AD for ≥2 years; (2) eczema area and severity index (EASI) score ≥12; (3) body surface area (BSA) involvement ≥10%; (4) having a history of inadequate response to at least one of the following 3 treatment categories for ≥4 weeks: A, emollients in combination with at least one of the following: TCS, antibiotics, or topical immune modulators; B, systemic steroids or phototherapy; C, ciclosporin or other immune modulators.

Up to Week 16, treatment discontinuation occurred in 10 of 37 subjects (27.0%) in the 2 mg group, 9 of 38 subjects (23.7%) in the 4 mg group, and 20 of 49 subjects (40.8%) in the placebo group. The most common reasons for discontinuation were "lack of efficacy" (4 of 37 subjects [10.8%] in the 2 mg group, 0 of 38 subjects [0%] in the 4 mg group, and 9 of 49 subjects [18.4%] in the placebo group), "adverse event" (1 of 37 subjects [2.7%] in the 2 mg group, 5 of 38 subjects [13.2%] in the 4 mg group, and 5 of 49 subjects [10.2%] in the placebo group), and "withdrawal by patient" (2 of 37 subjects [5.4%] in the 2 mg group, 2 of 38 subjects [5.3%] in the 4 mg group, and 3 of 49 subjects [6.1%] in the placebo group).

The ITT population included 20 Japanese subjects (6 subjects each in the 2 mg and 4 mg groups, and 8 subjects in the placebo group). In the Japanese subpopulation, up to Week 16, treatment discontinuation occurred in 0 of 6 subjects (0%) in the 2 mg group, 1 of 6 subjects (16.7%; "adverse events") in the 4 mg group, and 2 of 8 subjects (25.0%; "protocol violation" and "lack of efficacy") in the placebo group.

Table 4 shows the proportion of subjects achieving EASI50 at Week 16, the primary efficacy endpoint. While the difference between baricitinib 4 mg and placebo was statistically significant, the difference between baricitinib 2 mg and placebo was not. Table 4 also shows the outcomes for the Japanese subpopulation.

Table 4. Primary efficacy outcomes (ITT population, non-responder imputation [NRI])

		2 mg	4 mg	Placebo
Overall study population	Proportion of subjects achieving EASI50 at Week 16	56.8 (21/37)	60.5 (23/38)	36.7 (18/49)
	Difference compared with placebo [95% CI] *P*-value[a)]	20.0 [−1.1, 38.9] 0.065	23.8 [2.7, 42.2] 0.027	
Japanese subpopulation	Proportion of subjects achieving EASI50 at Week 16	66.7 (4/6)	83.3 (5/6)	37.5 (3/8)
	Difference compared with placebo [95% CI]	29.2 [−19.5, 62.7]	45.8 [−5.1, 73.3]	

% (n/N)

a) Two-sided chi-square test with a significance level of 5%. A step-wise approach was taken to adjust for multiplicity in hypothesis testing. First, the baricitinib 4 mg group was compared with the placebo group. If the test was statistically significant, then the baricitinib 2 mg group was compared with the placebo group.

Adverse events occurred in 19 of 37 subjects (51.4%) in the 2 mg group, 28 of 38 subjects (73.7%) in the 4 mg group, 25 of 49 subjects (51.0%) in the placebo group. Table 5 summarizes major adverse events.

No deaths occurred.

Serious adverse events occurred in 2 of 37 subjects in the 2 mg group (5.4%; bronchitis, cellulitis/staphylococcal infection/eczema), and 1 of 38 subjects in the 4 mg group (2.6%; large intestine polyp). A causal relationship to the study drug was ruled out for all the events.

Adverse events led to treatment discontinuation in 1 of 37 subjects (2.7%) in the 2 mg group, 5 of 38 subjects (13.2%) in the 4 mg group, and 5 of 49 subjects (10.2%) in the placebo group.

Adverse reactions occurred in 8 of 37 subjects (21.6%) in the 2 mg group, 12 of 38 subjects (31.6%) in the 4 mg group, and 10 of 49 subjects (20.4%) in the placebo group.

Table 5. Adverse events occurring in ≥2 subjects in any group (safety analysis set)

Adverse event	2 mg (N = 37)	4 mg (N = 38)	Placebo (N = 49)	Adverse event	2 mg (N = 37)	4 mg (N = 38)	Placebo (N = 49)
Headache	2 (5.4)	5 (13.2)	0	Eczema	1 (2.7)	1 (2.6)	2 (4.1)
Blood CPK increased	1 (2.7)	5 (13.2)	1 (2.0)	Lymphopenia	0	1 (2.6)	3 (6.1)
Nasopharyngitis	1 (2.7)	4 (10.5)	2 (4.1)	Somnolence	0	1 (2.6)	2 (4.1)
Dermatitis atopic	3 (8.1)	2 (5.3)	5 (10.2)	Cellulitis	2 (5.4)	0	3 (6.1)
Upper respiratory tract infection	1 (2.7)	2 (5.3)	1 (2.0)	Gastrooesophageal reflux disease	2 (5.4)	0	0
Procedural pain	0	2 (5.3)	1 (2.0)	Nausea	2 (5.4)	0	0
Subcutaneous abscess	0	2 (5.3)	1 (2.0)	Staphylococcal infection	2 (5.4)	0	0
White blood cell count decreased	0	2 (5.3)	0	n (%)			

In the Japanese subpopulation, adverse events occurred in 3 of 6 subjects (50.0%) in the 2 mg group, 6 of 6 subjects (100%) in the 4 mg group, and 4 of 8 subjects (50.0%) in the placebo group. Adverse events reported in ≥2 subjects in any group were nasopharyngitis (1 of 6 subjects [16.7%] in the 2 mg group, 3 of 6 subjects [50.0%] in the 4 mg group, and 1 of 8 subjects [12.5%] in the placebo group) and procedural pain (2 of 6 subjects [33.3%] in the 4 mg group and 1 of 8 subjects [12.5%] in the placebo group).

No deaths occurred.

A serious adverse event occurred in 1 of 6 subjects in the 4 mg group (16.7%; large intestine polyp), for which a causal relationship to the study drug was ruled out.

Adverse events led to treatment discontinuation in 1 of 6 subjects (16.7%) in the 2 mg group and 2 of 6 subjects (33.3%) in the 4 mg group.

An adverse reaction occurred in 1 of 6 subjects (16.7%) in the 4 mg group.

7.2 Phase III studies

7.2.1 Global study in patients with moderate to severe AD (monotherapy study, CTD 5.3.5.1.2, Study I4V-MC-JAHL [BREEZE-AD1] [November 2017 to December 2018])

A randomized, double-blind, placebo-controlled, parallel-group study was conducted in 9 countries or regions including Japan, Germany, and Czech Republic to evaluate the efficacy and safety of baricitinib in patients with moderate to severe AD[4)] who had a history of inadequate response to TCS of at least moderate potency[5)]

[4)] Patients with AD aged ≥18 years who meet all the following criteria: (1) having a diagnosis of AD according to the American Academy of Dermatology (AAD)'s guideline for ≥12 months prior to screening; (2) EASI score ≥16; (3) IGA score ≥3; (4) BSA involvement ≥10%; (5) patients have a documented history of inadequate response to TCS within 6 months prior to screening, or for whom TCS is not recommended because of safety reasons. Inadequate response to TCS is defined as meeting at least one of the following: (i) inability to achieve good disease control (e.g., IGA ≤2) after using TCS of at least moderate potency (or TCI may be added as needed) for 4 weeks or for the maximum duration recommended by the prescribing information in the package insert, whichever is shorter; or (ii) inadequately responded to systemic therapies for AD. Safety reasons are defined as a documented history of adverse reactions with the use of TCS (e.g., skin atrophy, allergic reactions, systemic effects) that outweigh the benefits of treatment.

[5)] A class having potency that is equivalent to the medium to strong class according to Japan's classification system.

or in whom TCS is not recommended because of safety reasons (target sample size, 600 subjects [120 subjects each in the 1 mg, 2 mg, and 4 mg groups, and 240 subjects in the placebo group]).

Subjects were to receive placebo or baricitinib 1 mg, 2 mg, or 4 mg[6)] once daily orally for 16 weeks. The protocol specified rules for concomitant AD therapies, and subjects were required to stop systemic therapies for AD at 4 weeks prior to baseline, and topical medications except emollients at 2 weeks prior to baseline. Subjects were to start applying emollients at ≥14 days prior to baseline and continue the use of concomitant emollients throughout the study. Rescue treatment[7)] was permitted for patients experiencing unacceptable symptoms.

A total of 624 subjects were randomly allocated to one of the treatment groups (127 subjects in the 1 mg group, 123 subjects in the 2 mg group, 125 subjects in the 4 mg group, and 249 subjects in the placebo group) stratified by baseline investigator's global assessment (IGA) score (3 versus 4) and by geographic region (Europe, Japan, or rest-of-world), and were included in the ITT population. The efficacy analysis population was the ITT population. The safety analysis set was defined as all randomized subjects who received at least 1 dose of the study drug and did not discontinue from the study due to "lost to follow-up" at the first post-baseline visit. The safety analysis set was consequently the same as the ITT population in this study.

Treatment discontinuation occurred in 11 of 127 subjects (8.7%) in the 1 mg group, 10 of 123 subjects (8.1%) in the 2 mg group, 5 of 125 subjects (4.0%) in the 4 mg group, and 23 of 249 subjects (9.2%) in the placebo group. The most common reasons for discontinuation were "withdrawal by patient" (5 of 127 subjects [3.9%] in the 1 mg group, 7 of 123 subjects [5.7%] in the 2 mg group, 2 of 125 subjects [1.6%] in the 4 mg group, and 10 of 249 subjects [4.0%] in the placebo group) and "lack of efficacy" (4 of 127 subjects [3.1%] in the 1 mg group, 1 of 123 subjects [0.8%] in the 2 mg group, 3 of 125 subjects [2.4%] in the 4 mg group, and 10 of 249 subjects [4.0%] in the placebo group).

The ITT population included 111 Japanese subjects (23 subjects in the 1 mg group, 21 subjects in the 2 mg group, 22 subjects in the 4 mg group, and 45 subjects in the placebo group). In the Japanese subpopulation, treatment discontinuation occurred in 1 of 23 subjects (4.3%) in the 1 mg group, 2 of 21 subjects (9.5%) in the 2 mg group, 0 of 22 subjects (0%) in the 4 mg group, and 3 of 45 subjects (6.7%) in the placebo group. The most common reason for discontinuation was "withdrawal by patient" (1 of 21 subjects [4.8%] in the 2 mg group and 2 of 45 subjects [4.4%] in the placebo group).

The co-primary efficacy endpoints were the proportion of subjects achieving IGA of 0 or 1 at Week 16 and the proportion of subjects achieving EASI75 at Week 16. Table 6 shows pairwise comparisons between the treatment groups. For both co-primary endpoints, the difference compared with placebo was statistically

6) Of the subjects allocated to the 4 mg group, those with renal impairment (eGFR ≥40 and <60 mL/min/1.73 m^2) received 2 mg.

7) Patients were to start with the use of triamcinolone 0.1% cream, hydrocortisone 2.5% ointment, or other equivalent potency TCS (use of TCI was also permitted but only for specific areas). The used of TCS of higher potency was allowed in patients who did not improve sufficiently after ≥7 days of the rescue treatment. If TCS rescue therapy failed to sufficiently control the symptoms, then use of systemic medications (oral corticosteroids or systemic nonsteroidal immunosuppressants) was allowed; however, study drug treatment was discontinued for the remainder of the study period.

significant for the baricitinib 2 mg and 4 mg groups, demonstrating the superiority of baricitinib 2 mg and 4 mg over placebo. In contrast, the difference between the baricitinib 1 mg and placebo groups was not significant for any of the co-primary endpoints after adjustment for multiplicity. Table 6 also shows the outcomes for the Japanese subpopulation.

Table 6. Primary efficacy outcomes (ITT population, NRI)

		1 mg	2 mg	4 mg	Placebo
Overall study population	Proportion of subjects achieving IGA 0 or 1 at Week 16	11.8 (15/127)	11.4 (14/123)	16.8 (21/125)	4.8 (12/249)
	Difference compared with placebo [95% CI] Adjusted *P*-value[a) c)]	7.0 [1.3, 14.1] —	6.6 [0.9, 13.7] 0.026	12.0 [5.5, 19.8] <0.001	
	Proportion of subjects achieving EASI75 at Week 16	17.3 (22/127)	18.7 (23/123)	24.8 (31/125)	8.8 (22/249)
	Difference compared with placebo [95% CI] Adjusted *P*-value[b) c)]	8.5 [1.5, 16.6] —	9.9 [2.6, 18.2] 0.026	16.0 [8.0, 24.7] <0.001	
Japanese subpopulation	Proportion of subjects achieving IGA 0 or 1 at Week 16	4.3 (1/23)	0 (0/21)	9.1 (2/22)	0 (0/45)
	Difference compared with placebo [95% CI]	4.3 [−4.3, 21.0]	0.0 [0.0, 0.0]	9.1 [−1.2, 27.8]	
	Proportion of subjects achieving EASI75 at Week 16	8.7 (2/23)	0 (0/21)	9.1 (2/22)	2.2 (1/45)
	Difference compared with placebo [95% CI]	6.5 [−4.8, 24.7]	−2.2 [−11.6, 13.3]	6.9 [−4.5, 25.7]	

% (n/N)
a) A logistic regression model with region, baseline IGA score, and treatment group as explanatory variables
b) A logistic regression model with region, baseline IGA score, treatment group, and baseline EASI score as explanatory variables
c) A 2-sided significance of 5%. A graphical approach (*Biom J.* 2011;53:894-913) was used for adjustment of multiplicity [see Section 10 for details of the approach]

Adverse events occurred in 69 of 127 subjects (54.3%) in the 1 mg group, 71 of 123 subjects (57.7%) in the 2 mg group, 73 of 125 subjects (58.4%) in the 4 mg group, and 135 of 249 subjects (54.2%) in the placebo group. Table 7 summarizes major adverse events.

No deaths occurred.

Serious adverse events occurred in 1 of 127 subjects (0.8%) in the 1 mg group, 2 of 125 subjects (1.6%) in the 4 mg group, and 6 of 249 subjects (2.4%) in the placebo group. A causal relationship to the study drug could not be ruled out for the following events: dermatitis atopic in 1 subject in the 1 mg group and papillary thyroid cancer in 1 subject in the placebo group.

Adverse events led to treatment discontinuation in 2 of 127 subjects (1.6%) in the 1 mg group, 1 of 123 subjects (0.8%) in the 2 mg group, 1 of 125 subjects (0.8%) in the 4 mg group, and 4 of 249 subjects (1.6%) in the placebo group.

Adverse reactions occurred in 21 of 127 subjects (16.5%) in the 1 mg group, 21 of 123 subjects (17.1%) in the 2 mg group, 29 of 125 subjects (23.2%) in the 4 mg group, and 30 of 249 subjects (12.0%) in the placebo group.

Table 7. Adverse events occurring in ≥2% of subjects in any group (safety analysis set)

Adverse event	1 mg (N = 127)	2 mg (N = 123)	4 mg (N = 125)	Placebo (N = 249)	Adverse event	1 mg (N = 127)	2 mg (N = 123)	4 mg (N = 125)	Placebo (N = 249)
Nasopharyngitis	22 (17.3)	12 (9.8)	12 (9.6)	26 (10.4)	Influenza	1 (0.8)	4 (3.3)	2 (1.6)	4 (1.6)
Headache	7 (5.5)	14 (11.4)	10 (8.0)	16 (6.4)	Acne	3 (2.4)	3 (2.4)	2 (1.6)	3 (1.2)
Upper respiratory tract infection	1 (0.8)	3 (2.4)	4 (3.2)	6 (2.4)	Oral herpes	3 (2.4)	2 (1.6)	2 (1.6)	0
Urinary tract infection	1 (0.8)	2 (1.6)	4 (3.2)	4 (1.6)	Pharyngitis	0	4 (3.3)	1 (0.8)	1 (0.4)
Herpes simplex	3 (2.4)	1 (0.8)	4 (3.2)	2 (0.8)	Pyrexia	1 (0.8)	3 (2.4)	1 (0.8)	0
Blood CPK increase	1 (0.8)	1 (0.8)	4 (3.2)	2 (0.8)	Otitis externa	3 (2.4)	1 (0.8)	1 (0.8)	1 (0.4)
Diarrhoea	9 (7.1)	0	4 (3.2)	7 (2.8)	Metrorrhagia[a)]	0	0	1 (2.4)	0
Cough	0	0	4 (3.2)	2 (0.8)	Abdominal pain	2 (1.6)	3 (2.4)	0	1 (0.4)
Abdominal pain upper	1 (0.8)	2 (1.6)	3 (2.4)	1 (0.4)	Dermatitis atopic	3 (2.4)	1 (0.8)	0	2 (0.8)
Fatigue	1 (0.8)	1 (0.8)	3 (2.4)	1 (0.4)	Dysmenorrhoea[a)]	0	1 (2.4)	0	1 (1.0)
Kaposi's varicelliform eruption	0	1 (0.8)	3 (2.4)	0	Vaginal infection[a)]	0	1 (2.4)	0	0
Rhinitis	1 (0.8)	0	3 (2.4)	2 (0.8)	Dermatitis contact	3 (2.4)	0	0	1 (0.4)
Gastroenteritis	1 (0.8)	0	3 (2.4)	1 (0.4)	Joint swelling	3 (2.4)	0	0	0

n (%)
a) The number of female subjects was used as the denominator for the calculation: N = 49 (1 mg), N = 41 (2 mg), N = 42 (4 mg), and N = 101 (placebo)

In the Japanese subpopulation, adverse events occurred in 8 of 23 subjects (34.8%) in the 1 mg group, 14 of 21 subjects (66.7%) in the 2 mg group, 12 of 22 subjects (54.5%) in the 4 mg group, and 22 of 45 subjects (48.9%) in the placebo group. Table 8 summarizes major adverse events.

No deaths or serious adverse events occurred.

An adverse event led to treatment discontinuation in 1 of 21 subjects (4.8%) in the 2 mg group.

Adverse reactions occurred in 2 of 23 subjects (8.7%) in the 1 mg group, 3 of 21 subjects (14.3%) in the 2 mg group, 6 of 22 subjects (27.3%) in the 4 mg group, and 4 of 45 subjects (8.9%) in the placebo group.

Table 8. Adverse events occurring in ≥2 subjects in any group (safety analysis set, Japanese subpopulation)

Adverse event	1 mg (N = 23)	2 mg (N = 21)	4 mg (N = 22)	Placebo (N = 45)
Nasopharyngitis	3 (13.0)	3 (14.3)	3 (13.6)	5 (11.1)
Kaposi's varicelliform eruption	0	1 (4.8)	3 (13.6)	0
Acne	1 (4.3)	1 (4.8)	2 (9.1)	2 (4.4)
Folliculitis	0	2 (9.5)	1 (4.5)	0
Headache	1 (4.3)	2 (9.5)	0	1 (2.2)

n (%)

7.2.2 Global clinical study in patients with moderate to severe AD (monotherapy study, CTD 5.3.5.1.3, Study I4V-MC-JAHM [BREEZE-AD2] [November 2017 to December 2018])

A randomized, double-blind, placebo-controlled, parallel-group study was conducted in 10 countries or regions including Japan, Poland, and Australia to evaluate the efficacy and safety of baricitinib in patients with moderate to severe AD[4)] who had a history of inadequate response to TCS of at least moderate potency[5)] or in whom TCS is not recommended because of safety reasons (target sample size, 600 subjects [120 subjects each in the 1 mg, 2 mg, and 4 mg groups, and 240 subjects in the placebo group]).

Subjects were to receive placebo or baricitinib 1 mg, 2 mg, or 4 mg[6)] once daily orally for 16 weeks. The protocol specified rules for concomitant AD therapies, and subjects were required to stop systemic therapies for AD at 4 weeks prior to baseline, and topical medications except emollients at 2 weeks prior to baseline. Subjects were to start applying emollients at ≥14 days prior to baseline and continue the use of concomitant emollients throughout the study. Rescue treatment[7)] was permitted for patients experiencing unacceptable symptoms.

A total of 615 subjects were randomly allocated to one of the treatment groups (125 subjects in the 1 mg group, 123 subjects in the 2 mg group, 123 subjects in the 4 mg group, and 244 subjects in the placebo group), stratified by baseline IGA score (3 versus 4) and by geographic region (Europe, Japan, or rest-of-the world). The randomized subjects were included in the ITT population. The efficacy analysis population was the ITT population. Of the randomized subjects, 614 subjects who received at least 1 dose of the study drug and did not discontinue from the study due to "lost to follow-up" at the first post-baseline visit were included in the safety analysis set (124 subjects in the 1 mg group, 123 subjects in the 2 mg group, 123 subjects in the 4 mg group, and 244 subjects in the placebo group), and 1 subject in the 1 mg group was excluded from the analysis.

Treatment discontinuation occurred in 10 of 125 subjects (8.0%) in the 1 mg group, 10 of 123 subjects (8.1%) in the 2 mg group, 6 of 123 subjects (4.9%) in the 4 mg group, and 19 of 244 subjects (7.8%) in the placebo group. The most common reasons for discontinuation were "lack of efficacy" (2 of 125 subjects [1.6%] in the 1 mg group, 7 of 123 subjects [5.7%] in the 2 mg group, 3 of 123 subjects [2.4%] in the 4 mg group, and 10 of 244 subjects [4.1%] in the placebo group), "withdrawal by patient" (3 of 125 subjects [2.4%] in the 1 mg group, 1 of 123 subjects [0.8%] in the 2 mg group, 0 of 123 subjects [0%] in the 4 mg group, and 8 of 244 subjects [3.3%] in the placebo group), and "adverse event" (3 of 125 subjects [2.4%] in the 1 mg group, 2 of 123 subjects [1.6%] in the 2 mg group, 2 of 123 subjects [1.6%] in the 4 mg group, and 1 of 244 subjects [0.4%] in the placebo group).

The ITT population included 112 Japanese subjects (22 subjects in the 1 mg group, 22 subjects in the 2 mg group, 23 subjects in the 4 mg group, and 45 subjects in the placebo group). In the Japanese subpopulation, treatment discontinuation occurred in 2 of 22 subjects (9.1%) in the 1 mg group, 1 of 22 subjects (4.5%) in the 2 mg group, 1 of 23 subjects (4.3%) in the 4 mg group, and 3 of 45 subjects (6.7%) in the placebo group. The most common reasons for discontinuation were "lack of efficacy" (1 of 22 subjects [4.5%] in the 2 mg group and 2 of 45 subjects [4.4%] in the placebo group), "withdrawal by patient" (1 of 22 subjects [4.5%] in the 1 mg group and 1 of 45 subjects [2.2%] in the placebo group), and "adverse event" (1 of 22 subjects [4.5%] in the 1 mg group and 1 of 23 subjects [4.3%] in the 4 mg group).

The co-primary efficacy endpoints were the proportion of subjects achieving IGA 0 or 1 at Week 16 and the proportion of subjects achieving EASI75 at Week 16. Table 9 shows pairwise comparisons between the groups. For both co-primary endpoints, the difference compared with placebo was statistically significant for the baricitinib 2 mg and 4 mg groups, demonstrating the superiority of baricitinib 2 mg and 4 mg over placebo. In

contrast, the difference between the baricitinib 1 mg and placebo groups was not significant for any of the co-primary endpoints after adjustment for multiplicity. Table 9 also shows the outcomes for the Japanese subpopulation.

Table 9. Primary efficacy outcomes (ITT population, NRI)

		1 mg	2 mg	4 mg	Placebo
Overall study population	Proportion of subjects achieving IGA 0 or 1 at Week 16	8.8 (11/125)	10.6 (13/123)	13.8 (17/123)	4.5 (11/244)
	Difference compared with placebo [95% CI] Adjusted *P*-value[a) c)]	4.3 [−0.8, 10.9] —	6.1 [0.6, 13.0] 0.041	9.3 [3.3, 16.8] 0.002	
	Proportion of subjects achieving EASI75 at Week 16	12.8 (16/125)	17.9 (22/123)	21.1 (26/123)	6.1 (15/244)
	Difference compared with placebo [95% CI] Adjusted *P*-value[b) c)]	6.7 [0.6, 14.0] —	11.7 [4.9, 19.8] 0.041	15.0 [7.7, 23.4] 0.002	
Japanese subpopulation	Proportion of subjects achieving IGA 0 or 1 at Week 16	4.5 (1/22)	0 (0/22)	4.3 (1/23)	0 (0/45)
	Difference compared with placebo [95% CI]	4.5 [−4.2, 21.8]	0.0 [0.0, 0.0]	4.3 [−4.3, 21.0]	
	Proportion of subjects achieving EASI75 at Week 16	9.1 (2/22)	0 (0/22)	13.0 (3/23)	0 (0/45)
	Difference compared with placebo [95% CI]	9.1 [−1.2, 27.8]	0.0 [0.0, 0.0]	13.0 [1.5, 32.1]	

% (n/N)
a) A logistic regression model with region, baseline IGA score, and treatment group as explanatory variables
b) A logistic regression model with region, baseline IGA score, treatment group, and baseline EASI score as explanatory variables
c) A 2-sided significance of 5%. A graphical approach (*Biom J.* 2011;53:894-913) was used for adjustment of multiplicity [see Section 10 for details of the approach]

Adverse events occurred in 66 of 124 subjects (53.2%) in the 1 mg group, 71 of 123 subjects (57.7%) in the 2 mg group, 66 of 123 subjects (53.7%) in the 4 mg group, and 137 of 244 subjects (56.1%) in the placebo group. Table 10 shows major adverse events.

No deaths occurred.

Serious adverse events occurred in 9 of 124 subjects (7.3%) in the 1 mg group, 3 of 123 subjects (2.4%) in the 2 mg group, 1 of 123 subjects (0.8%) in the 4 mg group, and 9 of 244 subjects (3.7%) in the placebo group. Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 4 subjects in the 1 mg group (lymphadenopathy/eczema herpeticum, peritonsillitis, drug eruption, and angioedema), 1 subject in the 2 mg group (dermatitis atopic), 1 subject in the 4 mg group (tonsillitis), and 2 subjects in the placebo group (eczema herpeticum in 2 subjects).

Adverse events led to treatment discontinuation in 7 of 124 subjects (5.6%) in the 1 mg group, 3 of 123 subjects (2.4%) in the 2 mg group, 2 of 123 subjects (1.6%) in the 4 mg group, and 2 of 244 subjects (0.8%) in the placebo group.

Adverse reactions occurred in 28 of 124 subjects (22.6%) in the 1 mg group, 21 of 123 subjects (17.1%) in the 2 mg group, 26 of 123 subjects (21.1%) in the 4 mg group, and 31 of 244 subjects (12.7%) in the placebo group.

Table 10. Adverse events occurring in ≥2% of subjects in any group (safety analysis set)

Adverse event	1 mg (N = 124)	2 mg (N = 123)	4 mg (N = 123)	Placebo (N = 244)	Adverse event	1 mg (N = 124)	2 mg (N = 123)	4 mg (N = 123)	Placebo (N = 244)
Headache	6 (4.8)	9 (7.3)	11 (8.9)	5 (2.0)	Hypertension	1 (0.8)	2 (1.6)	1 (0.8)	6 (2.5)
Nasopharyngitis	13 (10.5)	16 (13.0)	10 (8.1)	30 (12.3)	Nausea	1 (0.8)	2 (1.6)	1 (0.8)	5 (2.0)
Blood CPK increased	4 (3.2)	1 (0.8)	7 (5.7)	1 (0.4)	Pyrexia	2 (1.6)	1 (0.8)	1 (0.8)	8 (3.3)
Upper respiratory tract infection	6 (4.8)	5 (4.1)	4 (3.3)	5 (2.0)	Dizziness	0	1 (0.8)	1 (0.8)	7 (2.9)
Abdominal pain upper	3 (2.4)	4 (3.3)	4 (3.3)	7 (2.9)	Oral herpes	1 (0.8)	0	1 (0.8)	6 (2.5)
Herpes simplex	2 (1.6)	7 (5.7)	3 (2.4)	2 (0.8)	Pruritus	1 (0.8)	0	1 (0.8)	5 (2.0)
Diarrhoea	2 (1.6)	3 (2.4)	3 (2.4)	4 (1.6)	Superinfection bacterial	0	3 (2.4)	0	1 (0.4)
Abdominal pain	0	1 (0.8)	3 (2.4)	3 (1.2)	Conjunctivitis allergic	3 (2.4)	1 (0.8)	0	1 (0.4)
AST increased	1 (0.8)	0	3 (2.4)	0	Pain in extremity	3 (2.4)	1 (0.8)	0	0
Folliculitis	2 (1.6)	2 (1.6)	2 (1.6)	7 (2.9)	Angioedema	3 (2.4)	0	0	1 (0.4)
Pharyngitis	0	2 (1.6)	2 (1.6)	5 (2.0)	Dysmenorrhoea[a)]	1 (2.3)	0	0	2 (2.2)
Skin infection	3 (2.4)	0	2 (1.6)	1 (0.4)					

n (%)

a) The number of female subjects was used as the denominator for the calculation: N = 44 (1 mg), N = 58 (2 mg), N = 41 (4 mg), and N = 90 (placebo)

In the Japanese subpopulation, adverse events occurred in 14 of 22 subjects (63.6%) in the 1 mg group, 14 of 22 subjects (63.6%) in the 2 mg group, 12 of 23 subjects (52.2%) in the 4 mg group, and 27 of 45 subjects (60.0%) in the placebo group. Table 11 summarizes major adverse events.

No deaths occurred.

Serious adverse events occurred in 1 of 22 subjects (4.5%) in the 1 mg group, 1 of 23 subjects (4.3%) in the 4 mg group, and 3 of 45 subjects (6.7%) in the placebo group. A causal relationship to the study drug could not be ruled out for tonsillitis in 1 subject in the 4 mg group.

Adverse events led to treatment discontinuation in 1 of 22 subjects (4.5%) in the 1 mg group and 1 of 23 subjects (4.3%) in the 4 mg group.

Adverse reactions occurred in 5 of 22 subjects (22.7%) in the 1 mg group, 2 of 22 subjects (9.1%) in the 2 mg group, 6 of 23 subjects (26.1%) in the 4 mg group, and 8 of 45 subjects (17.8%) in the placebo group.

Table 11. Adverse events occurring in ≥2 subjects in any group (safety analysis set, Japanese subpopulation)

Adverse event	1 mg (N = 22)	2 mg (N = 22)	4 mg (N = 23)	Placebo (N = 45)	Adverse event	1 mg (N = 22)	2 mg (N = 22)	4 mg (N = 23)	Placebo (N = 45)
Nasopharyngitis	5 (22.7)	6 (27.3)	6 (26.1)	8 (17.8)	Furuncle	2 (9.1)	0	0	0
Blood creatinine increased	0	0	2 (8.7)	0	Contusion	2 (9.1)	0	0	0
Headache	1 (4.5)	2 (9.1)	1 (4.3)	1 (2.2)	Folliculitis	1 (4.5)	0	0	2 (4.4)
Blood CPK increased	2 (9.1)	0	1 (4.3)	0	Diarrhoea	0	0	0	2 (4.4)
Pharyngitis	0	1 (4.5)	0	2 (4.4)	Gastritis	0	0	0	2 (4.4)
Acne	2 (9.1)	0	0	1 (2.2)	Dermatitis atopic	0	0	0	2 (4.4)

n (%)

7.2.3 Global clinical study in patients with moderate to severe AD (TCS combination study, CTD 5.3.5.1.4, Study I4V-MC-JAIY [BREEZE-AD7] [November 2018 to August 2019])

A randomized, double-blind, placebo-controlled, parallel-group study was conducted in 10 countries or regions including Japan, South Korea, and Germany to evaluate the efficacy and safety of baricitinib in combination

with TCS in patients with moderate to severe AD[8)] who had a history of inadequate response to TCS of at least moderate potency[5)] (target sample size, 300 subjects; 100 subjects each per group).

Subjects were to receive placebo or baricitinib 2 mg, 4 mg[6)] once daily orally for 16 weeks. The protocol specified rules for concomitant AD therapies, and subjects were required to stop systemic therapies for AD at 4 weeks prior to baseline, and topical medications except emollients at 2 weeks prior to baseline. Subjects were to start applying emollients at ≥14 days prior to baseline and continue the use of concomitant emollients throughout the study. Subjects were instructed to start with the use of TCS from baseline, until symptoms subsided.[9)] Rescue treatment[10)] was permitted after Week 2 for subjects experiencing unacceptable symptoms.

A total of 329 subjects were randomly allocated to one of the treatment groups (109 subjects in the 2 mg group, 111 subjects in the 4 mg group, and 109 subjects in the placebo group), stratified by baseline IGA score (3 versus 4) and by geographic region (Europe, Japan, or rest-of-the-world). The randomized subjects were included in the ITT population. The efficacy analysis population was the ITT population. Of the randomized subjects, 328 subjects who received at least 1 dose of the study drug and did not discontinue from the study due to "lost to follow-up" at the first post-baseline visit were included in the safety analysis set (109 subjects in the 2 mg group, 111 subjects in the 4 mg group, and 108 subjects in the placebo group), and 1 subject in the placebo group was excluded from the analysis.

Treatment discontinuation occurred in 9 of 109 subjects (8.3%) in the 2 mg group, 4 of 111 subjects (3.6%) in the 4 mg group, and 7 of 109 subjects (6.4%) in the placebo group. The most common reasons for discontinuation were "withdrawal by patient" (5 of 109 subjects [4.6%] in the 2 mg group, 1 of 111 subjects [0.9%] in the 4 mg group, and 3 of 109 subjects [2.8%] in the placebo group), "lack of efficacy" (3 of 109 subjects [2.8%] in the 2 mg group, 0 of 111 subjects [0%] in the 4 mg group, and 2 of 109 subjects [1.8%] in the placebo group), and "adverse event" (1 of 109 subjects [0.9%] in the 2 mg group, 3 of 111 [2.7%] in the 4 mg group, and 0 of 109 subjects [0%] in the placebo group).

The ITT population included 63 Japanese subjects (20 subjects in the 2 mg group, 22 subjects in the 4 mg group, and 21 subjects in the placebo group). In the Japanese subpopulation, treatment discontinuation occurred in 0 of 20 subjects (0%) in the 2 mg group, 2 of 22 subjects (9.1%; due to "adverse event" for both subjects) in the 4 mg group, and 0 of 21 subjects (0%) in the placebo group.

[8)] Patients with AD aged ≥18 years who meet all the following criteria: (1) having a diagnosis of AD according to the AAD's guideline for ≥12 months prior to screening; (2) EASI score ≥16; (3) IGA score ≥3; (4) BSA involvement ≥10%; (5) patients have a documented history of inadequate response to TCS within 6 months prior to screening. Inadequate response to TCS is defined as meeting at least one of the following: (i) inability to achieve good disease control (e.g., IGA ≤2) after using TCS of at least moderate potency (or TCI may be added as needed) for 4 weeks or for the maximum duration recommended by the prescribing information in the package insert, whichever is shorter; or (ii) inadequately responded to systemic therapies for AD.

[9)] Patients were to start with the use of triamcinolone 0.1% cream (or equivalent-potency TCS, which is equivalent to the medium to strong class according to Japan's classification system) to the areas of active dermatitis once daily until symptoms subsided. Then patients were to switch to hydrocortisone 2.5% ointment (or equivalent-potency TCS, which is equivalent to the weak to medium class according to Japan's classification system) once daily for 7 days and then stop. If lesions reappeared, treatment with triamcinolone 0.1% cream (or equivalent-potency TCS) or hydrocortisone 2.5% ointment (or equivalent-potency TCS) was to be resumed. If still not resolving with these TCS, rescue treatment with high- or ultra-high potency TCS (equivalent to the strong to very strong class according to Japan's classification system) was to be considered.

[10)] To initiate rescue treatment, TCS of high potency or stronger was to be used first. In subjects with insufficient improvement, systemic medications (oral corticosteroids or systemic nonsteroidal immunosuppressants) was allowed; however, subjects receiving a systemic therapy were required to discontinue study drug treatment for the remainder of the study period.

The co-primary efficacy endpoints were the proportion of subjects achieving IGA 0 or 1 at Week 16 and the proportion of subjects achieving EASI75 at Week 16. Table 12 shows pairwise comparisons between the groups. The difference between the baricitinib 4 mg and placebo group was statistically significant for both co-primary endpoints, demonstrating the superiority of baricitinib 4 mg over placebo. On the other hand, the difference between the baricitinib 2 mg and placebo groups was not statistically significant for any of the co-primary endpoints after adjustment for multiplicity. Table 12 also shows the outcomes for the Japanese subpopulation.

Table 12. Primary efficacy outcomes (ITT population, NRI)

		2 mg	4 mg	Placebo
Overall study population	Proportion of subjects achieving IGA 0 or 1 at Week 16	23.9 (26/109)	30.6 (34/111)	14.7 (16/109)
	Difference compared with placebo [95% CI] Adjusted *P*-value[a) c)]	9.2 [−1.4, 19.5] 0.083	16.0 [4.9, 26.6] 0.005	
	Proportion of subjects achieving EASI75 at Week 16	43.1 (47/109)	47.7 (53/111)	22.9 (25/109)
	Difference compared with placebo [95% CI] Adjusted *P*-value[b) c)]	20.2 [7.7, 31.8] —	24.8 [12.2, 36.3] 0.005	
Japanese subpopulation	Proportion of subjects achieving IGA 0 or 1 at Week 16	15.0 (3/20)	9.1 (2/22)	9.5 (2/21)
	Difference compared with placebo [95% CI]	5.5 [−16.2, 27.6]	−0.4 [−20.9, 19.5]	
	Proportion of subjects achieving EASI75 at Week 16	55.0 (11/20)	22.7 (5/22)	19.0 (4/21)
	Difference compared with placebo [95% CI]	36.0 [6.4, 58.3]	3.7 [−20.8, 27.3]	

% (n/N)
a) A logistic regression model with region, baseline IGA score, and treatment group as explanatory variables
b) A logistic regression model with region, baseline IGA score, treatment group, and baseline EASI score as explanatory variables
c) A 2-sided significance of 5%. A graphical approach (*Biom J*. 2011;53:894-913) was used for adjustment of multiplicity [see Section 10 for details of the approach]

Adverse events occurred in 61 of 109 subjects (56.0%) in the 2 mg group, 64 of 111 subjects (57.7%) in the 4 mg group, and 41 of 108 subjects (38.0%) in the placebo group. Table 13 summarizes major adverse events.

No deaths occurred.

Serious adverse events occurred in 2 of 109 subjects (1.8%) in the 2 mg group, 4 of 111 subjects (3.6%) in the 4 mg group, and 4 of 108 subjects (3.7%) in the placebo group. Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 1 subject in the 2 mg group (dermatitis atopic), 1 subject in the 4 mg group (pulmonary embolism), and 1 subject in the placebo group (eye infection toxoplasmal).

Adverse events led to treatment discontinuation in 5 of 111 subjects (4.5%) in the 4 mg group and 1 of 108 subjects (0.9%) in the placebo group.

Adverse reactions occurred in 23 of 109 subjects (21.1%) in the 2 mg group, 20 of 111 subjects (18.0%) in the 4 mg group, and 13 of 108 subjects (12.0%) in the placebo group.

Table 13. Adverse events occurring in ≥2% of subjects in any group (safety analysis set)

Adverse event	2 mg (N = 109)	4 mg (N = 111)	Placebo (N = 108)	Adverse event	2 mg (N = 109)	4 mg (N = 111)	Placebo (N = 108)
Nasopharyngitis	12 (11.0)	17 (15.3)	13 (12.0)	Diarrhoea	1 (0.9)	3 (2.7)	1 (0.9)
Folliculitis	4 (3.7)	6 (5.4)	0	Oropharyngeal pain	2 (1.8)	2 (1.8)	3 (2.8)
Oral herpes	4 (3.7)	4 (3.6)	0	Pyrexia	0	1 (0.9)	3 (2.8)
Acne	1 (0.9)	4 (3.6)	1 (0.9)	Oligomenorrhoea[a)]	0	1 (2.8)	0
Back pain	0	4 (3.6)	1 (0.9)	Blood CPK increased	3 (2.8)	0	0
Upper respiratory tract infection	8 (7.3)	3 (2.7)	2 (1.9)	Vaginal infection[a)]	1 (2.6)	0	0
Herpes simplex	1 (0.9)	3 (2.7)	3 (2.8)	Rhinitis allergic	0	0	3 (2.8)

n (%)
a) The number of female subjects was used as the denominator for the calculation: N = 39 (2 mg), N = 36 (4 mg), and N =38 (placebo)

In the Japanese subpopulation, adverse events occurred in 7 of 20 subjects (35.0%) in the 2 mg group, 13 of 22 subjects (59.1%) in the 4 mg group, and 5 of 21 subjects (23.8%) in the placebo group. Table 14 summarizes major adverse events.

No deaths occurred.

A serious adverse event occurred in 1 of 22 subjects (4.5%; cataract) in the 4 mg group. A causal relationship to the study drug was ruled out for this event.

Adverse events led to treatment discontinuation in 2 of 22 subjects (9.1%) in the 4 mg group.

Adverse reactions occurred in 2 of 20 subjects (10.0%) in the 2 mg group, 4 of 22 subjects (18.2%) in the 4 mg group, and 1 of 21 subjects (4.8%) in the placebo group.

Table 14. Adverse events occurring in ≥2 subjects in any group (safety analysis set, Japanese subpopulation)

Adverse event	2 mg (N = 20)	4 mg (N = 22)	Placebo (N = 21)
Nasopharyngitis	1 (5.0)	3 (13.6)	2 (9.5)
Folliculitis	1 (5.0)	2 (9.1)	0
Toxic skin eruption	0	2 (9.1)	0
Conjunctivitis allergic	0	0	2 (9.5)

n (%)

7.2.4 Global clinical study in patients with moderate to severe AD (TCS combination study, CTD 5.3.5.1.6, Study I4V-MC-JAIN [BREEZE-AD4] [ongoing since May 2018, data cut-off in [redacted] 20[redacted]], reference data)

A randomized, double-blind, placebo-controlled, parallel-group study was conducted in 14 countries or regions including Japan, Germany, and Brazil to evaluate the efficacy and safety of baricitinib in combination with TCS in patients with moderate to severe AD[11)] who had a history of inadequate response to TCS of at least

[11)] Patients with AD aged ≥18 years who meet all the following criteria: (1) having a diagnosis of AD according to the AAD's guideline for ≥12 months prior to screening; (2) EASI score ≥16; (3) IGA score ≥3; (4) BSA involvement ≥10%; (5) patients have a documented history of inadequate response to TCS within 6 months prior to screening; (6) patients have a documented history of inadequate response to or a contraindication to ciclosporin. An inadequate response to TCS is defined as an inability to achieve good disease control (e.g., IGA ≤2) with the use of TCS of at least moderate potency for 4 weeks or for the maximum duration recommended by the prescribing information in the package insert, whichever is shorter. A contraindication to ciclosporin is defined as follows: hypersensitivity to ciclosporin preparations; hypertension or other medical conditions uncontrolled with medication; unacceptable adverse reactions to ciclosporin; increased susceptibility to ciclosporin-induced renal/liver damage; increased risk of serious infections; or use of prohibited concomitant medications. An inadequate response to ciclosporin is defined as failure to obtain good disease control within 6 weeks (or duration specified in the prescribing information in the package insert) of treatment with ciclosporin at 2.5 to 5 mg/kg/day, or

moderate potency[5)] and to ciclosporin, or in whom ciclosporin is not recommended because of safety reasons (target sample size, 500 subjects [100 subjects in the 1 mg group, 200 subjects in the 2 mg group, 100 subjects in the 4 mg group, and 100 subjects in the placebo group]).

The study consisted of 2 periods: a double-blind period (up to Week 52) and a long-term (double-blind) extension period (Weeks 52 to 200). In the double-blind period, subjects were to receive placebo or baricitinib 1 mg, 2 mg, or 4 mg[6)] once daily orally. Concomitant therapies for AD were stopped: systemic therapies at 4 weeks prior to baseline, biologics at 5 times the half-life prior to baseline, and topical medications except emollients at 2 weeks prior to baseline. Subjects were to start applying emollients at ≥14 days prior to baseline and continue the use of concomitant emollients throughout the study. Subjects were instructed to start with the use of TCS from baseline and continue it until symptoms subsided.[9)] Rescue treatment was permitted in subjects experiencing unacceptable symptoms.[12)] In the long-term extension period, subjects were assigned to placebo or baricitinib 1 mg, 2 mg, or 4 mg[6)] once daily orally based on factors including the IGA score and the use of rescue treatment.

A total of 463 subjects were randomly allocated to one of the treatment groups (93 subjects in the 1 mg group, 185 subjects in the 2 mg group, 92 subjects in the 4 mg group, and 93 subjects in the placebo group), stratified by baseline IGA score (3 versus 4) and by geographic region. The randomized subjects were included in the ITT population. The efficacy analysis population was the ITT population. Of the randomized subjects, 462 subjects who received at least 1 dose of the study drug and did not discontinue from the study due to "lost to follow-up" at the first post-baseline visit (93 subjects in the 1 mg group, 184 subjects in the 2 mg group, 92 subjects in the 4 mg group, and 93 subjects in the placebo group) were included in the safety analysis set, and 1 subject in the 2 mg group was excluded from the analysis.

Up to Week 16, treatment discontinuation occurred in 13 of 93 subjects (14.0%) in the 1 mg group, 12 of 185 subjects (6.5%) in the 2 mg group, 7 of 92 subjects (7.6%) in the 4 mg group, and 21 of 93 subjects (22.6%) in the placebo group. The most common reasons for discontinuation were "lack of efficacy" (10 of 93 subjects [10.8%] in the 1 mg group, 7 of 185 subjects [3.8%] in the 2 mg group, 6 of 92 subjects [6.5%] in the 4 mg group, and 16 of 93 subjects [17.2%] in the placebo group) and "adverse event" (0 of 93 subjects [0%] in the 1 mg group, 3 of 185 subjects [1.6%] in the 2 mg group, 1 of 92 subjects [1.1%] in the 4 mg group, and 1 of 93 subjects [1.1%] in the placebo group).

The ITT population included 79 Japanese subjects (16 subjects in the 1 mg group, 32 subjects in the 2 mg group, 16 subjects in the 4 mg group, and 15 subjects in the placebo group). No subjects discontinued treatment up to Week 16.

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requiring ciclosporin at doses >5 mg/kg/day. In Japan, in addition to the above, patients who were eligible for ciclosporin treatment but who, or whose family members, did not give consent to ciclosporin treatment were also allowed to participate in the study.

[12)] Rescue treatment was to start with the use of high- or ultra-high-potency TCS and phototherapy. In subjects with insufficient improvement, systemic therapies (conventional systemic drugs or biologics) were allowed; however, study drug treatment was interrupted during phototherapy. Study drug treatment was discontinued in subjects receiving a systemic therapy as rescue treatment.

Table 15 shows the proportion of subjects achieving EASI75 at Week 16, the primary efficacy endpoint,[13)] and the proportion of subjects achieving IGA 0 or 1 at Week 16, the secondary endpoint. The difference between the baricitinib 4 mg and placebo groups was statistically significant for the primary endpoint, demonstrating the superiority of baricitinib 4 mg over placebo. In contrast, the differences between the baricitinib 2 mg and placebo groups and between the baricitinib 1 mg and placebo groups were not statistically significant for any of the endpoints after adjustment for multiplicity. Table 15 also shows the outcomes for the Japanese subpopulation.

Table 15. Efficacy outcomes (ITT population, NRI)

		1 mg	2 mg	4 mg	Placebo
Overall study population	Proportion of subjects achieving IGA 0 or 1 at Week 16	12.9 (12/93)	15.1 (28/185)	21.7 (20/92)	9.7 (9/93)
	Difference compared with placebo [95% CI]	3.2 [−6.2, 12.7]	5.5 [−3.4, 12.9]	12.1 [1.5, 22.5]	
	Proportion of subjects achieving EASI75 at Week 16 (*)	22.6 (21/93)	27.6 (51/185)	31.5 (29/92)	17.2 (16/93)
	Difference compared with placebo [95% CI] Adjusted *P*-value[a) b)]	5.4 [−6.2, 16.8] —	10.4 [−0.4, 19.7] 0.078	14.3 [1.9, 26.2] 0.032	
Japanese subpopulation	Proportion of subjects achieving IGA 0 or 1 at Week 16	12.5 (2/16)	18.8 (6/32)	18.8 (3/16)	0 (0/15)
	Difference compared with placebo [95% CI]	12.5 [−9.8, 36.0]	18.8 [−3.9, 35.3]	18.8 [−5.0, 43.0]	
	Proportion of subjects achieving EASI75 at Week 16	18.8 (3/16)	31.3 (10/32)	43.8 (7/16)	6.7 (1/15)
	Difference compared with placebo [95% CI]	12.1 [−14.1, 37.0]	24.6 [−2.1, 42.7]	37.1 [6.1, 60.8]	

% (n/N); *, primary endpoint

a) A logistic regression model with region, baseline IGA score, treatment group, and baseline EASI score as explanatory variables

b) A 2-sided significance of 5%. A graphical approach (*Biom J.* 2011;53:894-913) was used for adjustment of multiplicity [see Section 10 for details of the approach].

Up to Week 16, adverse events occurred in 58 of 93 subjects (62.4%) in the 1 mg group, 125 of 184 subjects (67.9%) in the 2 mg group, 69 of 92 subjects (75.0%) in the 4 mg group, and 50 of 93 subjects (53.8%) in the placebo group. Table 16 summarizes major adverse events.

No deaths occurred.

Serious adverse events occurred in 4 of 93 subjects (4.3%) in the 1 mg group, 3 of 184 subjects (1.6%) in the 2 mg group, 6 of 92 subjects (6.5%) in the 4 mg group, and 2 of 93 subjects (2.2%) in the placebo group. Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 1 subject in the 2 mg group (dermatitis atopic), 2 subjects in the 4 mg group (dermatitis atopic and staphylococcal infection), and 1 subject in the placebo group (dermatitis atopic/Bowen's disease).

Adverse events led to treatment discontinuation in 3 of 184 subjects (1.6%) in the 2 mg group, 1 of 92 subjects (1.1%) in the 4 mg group, and 1 of 93 subjects (1.1%) in the placebo group.

[13)] At the beginning of the study, the primary endpoint was originally defined as follows: the proportion of subjects achieving IGA 0 or 1 at Week 16 and the proportion of subjects achieving EASI75 at Week 16 in Japan, and the proportion of subjects achieving IGA 0 or 1 at Week 16 in other countries or regions. After the start of the study, based on the results from clinical studies of baricitinib in patients with AD, the primary endpoints in the blinded studies were changed to the proportion of subjects achieving EASI75 at Week 16 both in Japan and other countries.

Adverse reactions occurred in 25 of 93 subjects (26.9%) in the 1 mg group, 49 of 184 subjects (26.6%) in the 2 mg group, 25 of 92 subjects (27.2%) in the 4 mg group, and 22 of 93 subjects (23.7%) in the placebo group.

Table 16. Adverse events occurring in ≥3% of subjects in any group (up to Week 16, safety analysis set)

Adverse event	1 mg (N = 93)	2 mg (N = 184)	4 mg (N = 92)	Placebo (N = 93)	Adverse event	1 mg (N = 93)	2 mg (N = 184)	4 mg (N = 92)	Placebo (N = 93)
Nasopharyngitis	10 (10.8)	26 (14.1)	24 (26.1)	12 (12.9)	Nausea	0	7 (3.8)	2 (2.2)	0
Headache	8 (8.6)	11 (6.0)	7 (7.6)	6 (6.5)	Oropharyngeal pain	5 (5.4)	6 (3.3)	2 (2.2)	1 (1.1)
Influenza	3 (3.2)	8 (4.3)	6 (6.5)	2 (2.2)	Upper respiratory tract infection	1 (1.1)	6 (3.3)	2 (2.2)	0
Diarrhoea	1 (1.1)	6 (3.3)	5 (5.4)	3 (3.2)	Fatigue	2 (2.2)	2 (1.1)	2 (2.2)	3 (3.2)
Oral herpes	3 (3.2)	4 (2.2)	5 (5.4)	3 (3.2)	Cough	1 (1.1)	6 (3.3)	1 (1.1)	0
Abdominal pain upper	1 (1.1)	3 (1.6)	5 (5.4)	2 (2.2)	Blood CPK increased	3 (3.2)	2 (1.1)	1 (1.1)	2 (2.2)
Herpes simplex	0	4 (2.2)	4 (4.3)	1 (1.1)	Asthma	1 (1.1)	2 (1.1)	1 (1.1)	3 (3.2)
Oedema peripheral	0	0	4 (4.3)	0	Pharyngitis	0	2 (1.1)	1 (1.1)	3 (3.2)
Abdominal pain	1 (1.1)	6 (3.3)	3 (3.3)	3 (3.2)	Folliculitis	6 (6.5)	6 (3.3)	0	1 (1.1)
Urinary tract infection	1 (1.1)	4 (2.2)	3 (3.3)	0	Furuncle	0	2 (1.1)	0	3 (3.2)
Back pain	2 (2.2)	4 (2.2)	3 (3.3)	3 (3.2)	Dyspnoea	3 (3.2)	1 (0.5)	0	0
Conjunctivitis	1 (1.1)	2 (1.1)	3 (3.3)	1 (1.1)	Dry eye	0	0	0	3 (3.2)
Skin infection	1 (1.1)	1 (0.5)	3 (3.3)	1 (1.1)					

n (%)

In the Japanese subpopulation, up to Week 16, adverse events occurred in 5 of 16 subjects (31.3%) in the 1 mg group, 13 of 32 subjects (40.6%) in the 2 mg group, 9 of 16 subjects (56.3%) in the 4 mg group, and 5 of 15 subjects (33.3%) in the placebo group. Table 17 summarizes major adverse events.

No deaths occurred.

A serious adverse event occurred in 1 of 16 subjects (6.3%; intervertebral disc degeneration) in the 1 mg group, and a causal relationship to the study drug was ruled out for this event.

No adverse events led to treatment discontinuation.

Adverse reactions occurred in 3 of 16 subjects (18.8%) in the 1 mg group, 3 of 32 subjects (9.4%) in the 2 mg group, 1 of 16 subjects (6.3%) in the 4 mg group, and 1 of 15 subjects (6.7%) in the placebo group.

Table 17. Adverse events occurring in ≥2 subjects in any group (up to Week 16, safety analysis set, Japanese subpopulation)

Adverse event	1 mg (N = 16)	2 mg (N = 32)	4 mg (N = 16)	Placebo (N = 15)
Nasopharyngitis	0	5 (15.6)	6 (37.5)	2 (13.3)
Folliculitis	2 (12.5)	2 (6.3)	0	1 (6.7)
Abdominal pain	0	2 (6.3)	0	0
Oral herpes	0	2 (6.3)	0	0
Otitis externa	0	2 (6.3)	0	0

n (%)

7.2.5 Long-term extension study (CTD 5.3.5.1.5.1 to 5.3.5.1.5.2, Study I4V-MC-JAHN [BREEZE-AD3] [ongoing since March 2018, data cut-off in [redacted] 20[redacted]])

A randomized, double-blind, parallel-group study was conducted in 19 countries or regions including Japan, Germany, and Poland to evaluate the long-term efficacy and safety of baricitinib in patients with AD who had

completed one of the following studies: BREEZE-AD1, BREEZE-AD2, or BREEZE-AD7 (target sample size, 1,425 subjects). A cohort was added to evaluate baricitinib open-label in patients with AD[4] (target sample size, 250 subjects) who had not participated in any of the 3 originating studies (there were no participants from Japan).

As shown in Figure 3, the study consisted of 2 periods: Part 1 (up to Week 52) and Part 2 (Week 52-200). In Part 1, subjects were assigned to receive placebo or baricitinib 1 mg, 2 mg, or 4 mg[6] once daily orally based on factors including the IGA score at Week 16 (final visit) of the originating study. In the additional open-label cohort, subjects were to receive baricitinib 2 mg once daily orally. In Part 2, subjects (including those in the open-label 2 mg cohort) who received baricitinib 2 mg or 4 mg[6] in Part 1 and were eligible[14] for enrollment in a withdrawal and down-titration substudy at Week 52 were to be re-randomized and assigned to receive placebo or baricitinib 1 mg, 2 mg, or 4 mg[6] once daily orally. Ineligible subjects were to continue the dose assigned in Part 1. Subjects enrolled in the substudy were to be re-treated with the dosage regimen used in Part 1 if their IGA score had become ≥3. Subjects were instructed to use concomitant emollients throughout the treatment period. The concomitant use of TCS was also allowed at the investigator's discretion.[15]

[14] Subjects were eligible to enter the substudy if they met all of the following criteria: (1) IGA score ≤2 at Week 52; (2) no history of use of high- or ultra-high TCS in the previous 14 days; (3) not undergoing treatment interruption.

[15] Patients were to start with the use of triamcinolone 0.1% cream, hydrocortisone 2.5% ointment, or other equivalent-potency TCS (use of TCI was also permitted but only for specific areas). In patients who had insufficient improvement after ≥7 days of the rescue treatment, the use of a higher potency TCS was allowed.

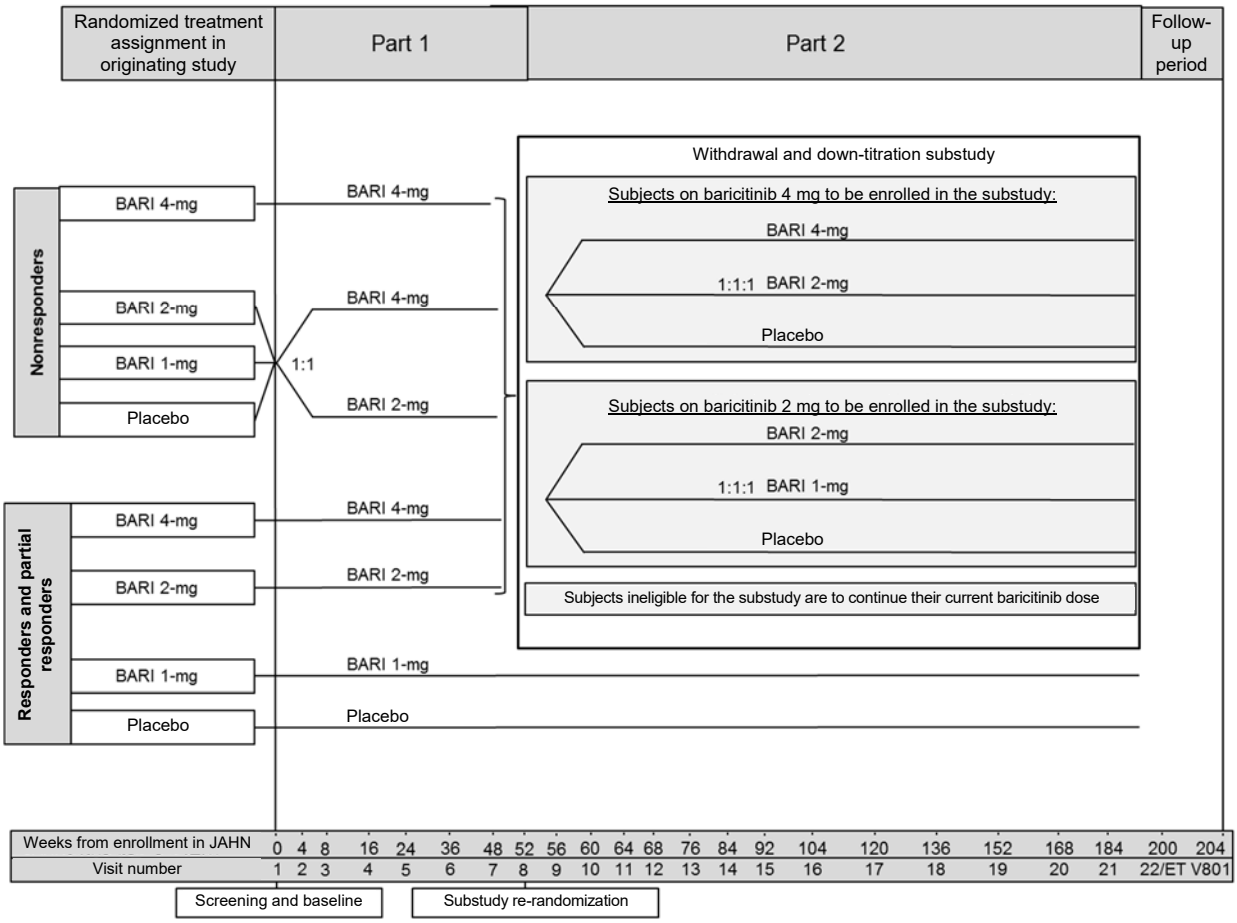


Figure 3. Design of the BREEZE-AD3 study
Responders: subjects who had an IGA 0 or 1 AND were not rescued in the originating study
Partial responders: subjects who had an IGA score of 2 AND were not rescued in the originating study
Non-responders: subjects who had an IGA score of 3 or 4 OR were rescued in the originating study

A total of 1,373 subjects[16] from the originating studies received at least 1 dose of the study drug, and all the subjects were included in the modified ITT (mITT) population: 45 subjects in the 1 mg group, 512 subjects in the 2 mg group (in the originating studies, 107 subjects were classified as responders/partial responders, and 405 subjects as non-responders), 730 subjects in the 4 mg group (in the originating studies, 133 subjects were classified as responders/partial responders, and 597 subjects as non-responders), and 86 subjects in the placebo group. The mITT population was used as the efficacy analysis population. The open-label cohort was added to the subjects from the originating studies (1,373 subjects + 247 subjects) for analyses, and a total of 1,620 subjects who received at least 1 dose of the study drug were included in the safety analysis set: 45 subjects in the 1 mg group, 759 subjects in the 2 mg group, 730 subjects in the 4 mg group, and 86 subjects in the placebo group.

In Part 1, in the mITT population, treatment discontinuation occurred in 12 of 45 subjects (26.7%) in the 1 mg group, 143 of 512 subjects (27.9%) in the 2 mg group, 213 of 730 subjects (29.2%) in the 4 mg group, and 13 of 86 subjects (15.1%) in the placebo group. The most common reasons for discontinuation were “lack of efficacy” (6 of 45 subjects [13.3%] in the 1 mg group, 90 of 512 subjects [17.6%] in the 2 mg group, 145 of

[16] The breakdown is as follows: 541 subjects from BREEZE-AD1, 540 subjects from BREEZE-AD2, and 292 subjects from BREEZE-AD7.

730 subjects [19.9%] in the 4 mg group, and 3 of 86 subjects [3.5%] in the placebo group) and “withdrawal by patient” (4 of 45 subjects [8.9%] in the 1 mg group, 41 of 512 subjects [8.0%] in the 2 mg group, 39 of 730 subjects [5.3%] in the 4 mg group, and 6 of 86 subjects [7.0%] in the placebo group).

The mITT population included 244 Japanese subjects (3 subjects in the 1 mg group, 89 subjects in the 2 mg group, 141 subjects in the 4 mg group, and 11 subjects in the placebo group). In Part 1, in the Japanese subpopulation, treatment discontinuation occurred in 15 of 89 subjects (16.9%) in the 2 mg group, 17 of 141 subjects (12.1%) in the 4 mg group, and 2 of 11 subjects (18.2%) in the placebo group. The most common reasons for discontinuation were “withdrawal by patient” (8 of 89 subjects [9.0%] in the 2 mg group, 6 of 141 subjects [4.3%] in the 4 mg group, and 1 of 11 subjects [9.1%] in the placebo group), “lack of efficacy” (5 of 89 subjects [5.6%] in the 2 mg group and 3 of 141 subjects [2.1%] in the 4 mg group), and “adverse event” (1 of 89 subjects [1.1%] in the 2 mg group and 7 of 141 subjects [5.0%] in the 4 mg group).

In Part 1, adverse events occurred in 26 of 45 subjects (57.8%) in the 1 mg group, 463 of 759 subjects (61.0%) in the 2 mg group, 468 of 730 subjects (64.1%) in the 4 mg group, and 39 of 86 subjects (45.3%) in the placebo group. Table 18 summarizes major adverse events.

A death occurred in the 4 mg group (gastrointestinal haemorrhage), and a causal relationship to the study drug was ruled out.

Serious adverse events occurred in 1 of 45 subjects (2.2%) in the 1 mg group, 31 of 759 subjects (4.1%) in the 2 mg group, 35 of 730 subjects (4.8%) in the 4 mg group, and 4 of 86 subjects (4.7%) in the placebo group. Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 7 subjects in the 2 mg group (dermatitis atopic in 3 subjects, eczema herpeticum in 2 subjects, pneumonia/hepatic failure/renal failure/pancreatic failure, and myocarditis) and 17 subjects in the 4 mg group (dermatitis atopic in 3 subjects, eczema herpeticum in 3 subjects, cellulitis, dermatitis atopic [4 cases]/skin bacterial infection [2 cases]/superinfection bacterial/thrombophlebitis, eczema herpeticum/staphylococcal skin infection/staphylococcal bacteraemia/thrombophlebitis, diverticulitis/colitis, superinfection bacterial, vasculitis, anaplastic large cell lymphoma T- and null-cell types, psoas abscess, eczema herpeticum/erysipelas, pulmonary embolism, and ventricular extrasystoles/sinus tachycardia).

Adverse events led to treatment discontinuation in 18 of 759 subjects (2.4%) in the 2 mg group and 24 of 730 subjects (3.3%) in the 4 mg group.

Adverse reactions occurred in 3 of 45 subjects (6.7%) in the 1 mg group, 131 of 759 subjects (17.3%) in the 2mg group, 148 of 730 subjects (20.3%) in the 4 mg group, and 6 of 86 subjects (7.0%) in the placebo group.

Table 18. Adverse events occurring in ≥3% of subjects in any group (Part 1, safety analysis set)

Adverse event	1 mg (N = 45)	2 mg (N = 759)	4 mg (N = 730)	Placebo (N = 86)	Adverse event	1 mg (N = 45)	2 mg (N = 759)	4 mg (N = 730)	Placebo (N = 86)
Nasopharyngitis	9 (20.0)	96 (12.6)	114 (15.6)	8 (9.3)	Headache	1 (2.2)	44 (5.8)	19 (2.6)	6 (7.0)
Upper respiratory tract infection	0	36 (4.7)	39 (5.3)	1 (1.2)	Gastroenteritis	2 (4.4)	13 (1.7)	16 (2.2)	0
Oral herpes	0	32 (4.2)	36 (4.9)	2 (2.3)	Pyrexia	2 (4.4)	12 (1.6)	15 (2.1)	0
Herpes simplex	1 (2.2)	18 (2.4)	31 (4.2)	2 (2.3)	Pharyngitis	0	18 (2.4)	14 (1.9)	3 (3.5)
Bronchitis	0	6 (0.8)	24 (3.3)	1 (1.2)	Cough	2 (4.4)	9 (1.2)	10 (1.4)	0
Influenza	0	30 (4.0)	20 (2.7)	2 (2.3)	Cystitis	2 (4.4)	3 (0.4)	8 (1.1)	0

n (%)

In Part 1, in the Japanese subpopulation, adverse events occurred in 2 of 3 subjects (66.7%) in the 1 mg group, 59 of 89 subjects (66.3%) in the 2 mg group, 94 of 141 subjects (66.7%) in the 4 mg group, and 3 of 11 subjects (27.3%) in the placebo group. Table 19 summarizes major adverse events.

No deaths occurred.

Serious adverse events occurred in 1 of 89 subjects (1.1%) in the 2 mg group, 3 of 141 subjects (2.1%) in the 4 mg group, and 1 of 11 subjects (9.1%) in the placebo group. A causal relationship to the study drug could not be ruled out for the events in 2 subjects in the 4 mg group (cellulitis and psoas abscess).

Adverse events led to treatment discontinuation in 5 of 141 subjects (3.5%) in the 4 mg group.

Adverse reactions occurred in 17 of 89 subjects (19.1%) in the 2 mg group, 31 of 141 subjects (22.0%) in the 4 mg group, and 1 of 11 subjects (9.1%) in the placebo group.

Table 19. Adverse events occurring in ≥3% of subjects in the 2 mg or 4 mg group (Part 1, safety analysis set, Japanese subpopulation)

Adverse event	1 mg (N = 3)	2 mg (N = 89)	4 mg (N = 141)	Placebo (N = 11)	Adverse event	1 mg (N = 3)	2 mg (N = 89)	4 mg (N = 141)	Placebo (N = 11)
Nasopharyngitis	0	17 (19.1)	31 (22.0)	1 (9.1)	Insomnia	0	3 (3.4)	3 (2.1)	0
Influenza	0	3 (3.4)	7 (5.0)	0	ALT increased	0	3 (3.4)	3 (2.1)	0
Herpes simplex	0	3 (3.4)	7 (5.0)	0	AST increased	0	3 (3.4)	2 (1.4)	0
Skin papilloma	0	2 (2.2)	6 (4.3)	0	Headache	0	3 (3.4)	1 (0.7)	0
Folliculitis	0	9 (10.1)	5 (3.5)	1 (9.1)	Pharyngitis	0	5 (5.6)	0	0
Acne	1 (33.3)	5 (5.6)	5 (3.5)	0	Dysmenorrhoea[a)]	–	1 (3.7)	0	0
Miliaria	0	3 (3.4)	3 (2.1)	0					

n (%)

No adverse events occurred in ≥2 subjects in the 1 mg group or the placebo group

a) The number of female subjects was used as the denominator for the calculation: N = 0 (1 mg), N = 27 (2 mg), N = 33 (4 mg), N = 3 (placebo)

7.R Outline of the review conducted by PMDA

7.R.1 Development plan

The applicant's explanation about the development plan for baricitinib:

Diagnostic criteria and treatment algorithms for AD specified in the clinical practice guidelines available in Japan are similar to those used in other countries, suggesting that there are no substantial differences in diagnostic and treatment strategies for AD between Japan and other countries (Clinical Practice Guidelines for the Management of Atopic Dermatitis 2018 [in Japanese]. *Jpn J Dermatol.* 2018;128:2431-2502, *J Am Acad Dermatol.* 2014;71:116-132, *J Eur Acad Dermatol Venereol.* 2018;32:850-878). Data including the results from clinical studies in healthy subjects and patients with RA have shown that there are no clear differences in

the pharmacokinetics of baricitinib between Japanese and non-Japanese populations that may affect the efficacy or safety of baricitinib (see Review Report of "Olumiant Tablets 2 mg and 4 mg" dated May 19, 2017).

On the basis of the above, the applicant considered it possible to evaluate the efficacy and safety of baricitinib in Japanese patients with AD by conducting global clinical studies in countries/regions including Japan to develop a clinical data package.

The details of the "patient population," "efficacy endpoints," "dosage regimen," and "concomitant treatments" determined for the phase III, global clinical study are presented in the sections below.

- **Patient population**

The mainstay of pharmacotherapy for AD consists of topical anti-inflammatory drugs. In addition to the regular use of emollients, it is important to choose a TCS of appropriate potency depending on the severity of the individual lesions (TCI is added as needed) and use the correct amount of the TCS for the required period of time in a precise manner. In patients with a history of inadequate response to these therapies, systemic treatment is considered. The use of intermittent oral ciclosporin or subcutaneous dupilumab may be an option, and the use of oral corticosteroids may also be considered for induction of remission in AD patients with acute exacerbation or severe or the most severe conditions (Clinical Practice Guidelines for the Management of Atopic Dermatitis 2018 [in Japanese]. *Jpn J Dermatol.* 2018;128:2431-2502).

In line with the above treatment strategy, in the phase III, global clinical studies (BREEZE-AD1, BREEZE-AD2, BREEZE-AD7, and BREEZE-AD4), the study population was defined as patients with moderate to severe AD (requiring systemic therapy) who had an inadequate response to conventional topical treatments (inability to achieve good disease control with the use of TCS of at least moderate potency[5)] for ≥4 weeks [or TCI may be added as needed]) and have a certain level of disease activity (meeting all of the following criteria: IGA score ≥3, EASI score ≥16, and BSA involvement ≥10%). Additionally, the BREEZE-AD1 and BREEZE-AD2 studies included patients for whom TCS is not recommended because of safety reasons (history of adverse reactions with the use of TCS, such as skin atrophy, allergic reactions, and systemic effects, that outweigh the benefits of treatment). In the BREEZE-AD4 study, to evaluate the efficacy and safety of baricitinib in patients with more severe AD, a history of inadequate response to ciclosporin or intolerance to ciclosporin (i.e., its use is not recommended because of safety reasons) was also included in the eligibility criteria.

- **Efficacy endpoints**

The goal of AD treatment is to reduce the signs and symptoms of AD. The co-primary endpoints for the phase III, global clinical studies were the following measures: the IGA score that provides a global clinical assessment of skin lesions by the physician, and the EASI score that is a physician assessment tool to measure the severity and surface area of the skin lesions for each body region on a numeric scale. In addition, the itch numerical rating scale (itch NRS) was selected as a secondary endpoint to measure itch as an important subjective

symptom for AD. The itch NRS is a patient assessment scale to comprehensively assess the severity of itch in patients with AD.

- **Dosage regimen**

In the phase II, global clinical study evaluating the efficacy and safety of baricitinib 2 mg or 4 mg once daily in combination with TCS in patients with moderate to severe AD who had an inadequate response to conventional treatments [see Section 7.1.1], the primary endpoint outcomes, the proportion of subjects achieving EASI50 at Week 16, showed that the difference between the baricitinib 4 mg and placebo groups was statistically significant. In contrast, the difference between the baricitinib 2 mg and placebo groups was not statistically significant; however, baricitinib 2 mg was more effective than placebo in reaching EASI50. Since outcomes for IGA and other secondary endpoints suggested a certain level of efficacy at both dose levels, a dosage regimen of 2 mg or 4 mg once daily was selected for the phase III studies. Furthermore, in the BREEZE-AD1 and BREEZE-AD2 studies, a lower dose level, a 1-mg once daily regimen was established to determine the minimum effective dose.

The exposure to baricitinib increases with decreasing renal function [see Section 6.2.1]; therefore, when patients with moderate renal impairment were assigned to the 4 mg group, 2 mg was to be administered instead, so that baricitinib exposures in the patient population would not exceed those in patients with normal renal function or mild renal impairment on baricitinib 4 mg.

- **Concomitant treatments**

Given that continued use of emollients to improve or maintain the skin barrier function is essential in the treatment of AD, the study was designed to require use of emollients as background treatment.

There were restrictions to the use of topical anti-inflammatory drugs in the BREEZE-AD1 and BREEZE-AD2 studies evaluating the efficacy and safety of baricitinib monotherapy. Concomitant use of TCS and TCI was not allowed for 2 weeks prior to baseline; however, rescue treatment was allowed in subjects who were experiencing unacceptable symptoms. In the context of the treatment strategy for AD, baricitinib is expected to be used in combination with TCS in routine clinical practice; therefore, the efficacy and safety of baricitinib in combination with TCS were evaluated in the BREEZE-AD7 and BREEZE-AD4 studies. Subjects were required to stop using concomitant TCS and TCI for 2 weeks prior to baseline, and to resume TCS treatment from baseline until symptoms subsided.

PMDA accepted the applicant's explanation, and concluded that it is possible to evaluate the efficacy and safety of baricitinib in patients with AD based on the clinical data package submitted, focusing on the results of the phase III, global clinical studies in which Japanese patients participated. Since emollients and topical anti-inflammatory drugs are used concomitantly as the standard therapies for AD in Japan, the following sections discuss the efficacy review primarily focusing on the results from the BREEZE-AD7 and BREEZE-AD4 studies, which evaluated the efficacy and safety of baricitinib in combination with TCS.

7.R.2 Efficacy

The applicant's explanation about the efficacy of baricitinib:

In the BREEZE-AD1 and BREEZE-AD2 studies, which evaluated the efficacy and safety of baricitinib monotherapy in patients with AD who had a history of inadequate response to TCS of at least moderate potency[5)] or in whom TCS is not recommended because of safety reasons, the co-primary endpoints were the proportion of subjects achieving IGA 0 or 1 at Week 16 and the proportion of subjects achieving EASI75 at Week 16. For both co-primary endpoints, the difference versus placebo was statistically significant for the baricitinib 2 mg and 4 mg groups, demonstrating the superiority of baricitinib 2 mg and 4 mg over placebo (Table 6 and Table 9).

In the BREEZE-AD7 study, which evaluated the efficacy and safety of baricitinib in combination with TCS in patients with AD who had a history of inadequate response to TCS of at least moderate potency,[5)] the difference between the baricitinib 4 mg and placebo groups was statistically significant for both co-primary endpoints, i.e., the proportion of subjects achieving IGA 0 or 1 at Week 16 and the proportion of subjects achieving EASI75 at Week 16, demonstrating the superiority of baricitinib 4 mg over placebo (Table 12).

In the BREEZE-AD4 study, which evaluated the efficacy and safety of baricitinib in combination with TCS in patients with AD who had a history of inadequate response to TCS of at least moderate potency[5)] and to ciclosporin, or in whom ciclosporin is not recommended because of safety reasons, the difference between the baricitinib 4 mg and placebo groups was statistically significant for the primary endpoint, i.e., the proportion of subjects achieving EASI75 at Week 16, demonstrating the superiority of baricitinib 4 mg over placebo (Table 15).

Table 20 shows the outcomes of key efficacy endpoints for the BREEZE-AD7 and BREEZE-AD4 studies. In both studies, for all endpoints, the outcomes tended to be consistently higher in the 4 mg group than in the placebo group up to the evaluation time point for the primary endpoint (Week 16). For most of the endpoints, 2 mg tended to be more effective than placebo even though 2 mg was not as significant as 4 mg in terms of the magnitude of response or time to response. At Week 16 and thereafter, the proportion of subjects achieving the target for each endpoint decreased in the baricitinib groups but increased in the placebo group; as a result, the difference compared with placebo tended to decrease. However, the baricitinib groups tended to be superior to placebo throughout the treatment period when the percent change from baseline in EASI score was used as an index (Figure 4).

Table 20. Outcomes of key efficacy endpoints in studies evaluating baricitinib in combination with TCS (ITT population, NRI, overall study population)

	Time point	BREEZE-AD7			BREEZE-AD4			
		2 mg	4 mg	Placebo	1 mg	2 mg	4 mg	Placebo
Proportion of subjects achieving IGA 0 or 1	Week 2	7.3 (8/109)	11.7 (13/111)	7.3 (8/109)	7.5 (7/93)	4.3 (8/185)	7.6 (7/92)	2.2 (2/93)
	Week 4	17.4 (19/109)	19.8 (22/111)	5.5 (6/109)	7.5 (7/93)	9.7 (18/185)	16.3 (15/92)	4.3 (4/93)
	Week 8	23.9 (26/109)	25.2 (28/111)	7.3 (8/109)	9.7 (9/93)	12.4 (23/185)	19.6 (18/92)	9.7 (9/93)
	Week 16 (*)	23.9 (26/109)	30.6 (34/111)	14.7 (16/109)	12.9 (12/93)	15.1 (28/185)	21.7 (20/92)	9.7 (9/93)
	Week 32	—	21.6 (22/102)[a)]	—	15.1 (14/93)	14.1 (26/185)	13.0 (12/92)	14.0 (13/93)
	Week 52	—	23.5 (24/102)[a)]	—	16.1 (15/93)	12.4 (23/185)	16.3 (15/92)	14.0 (13/93)
Proportion of subjects achieving EASI75	Week 2	19.3 (21/109)	26.1 (29/111)	8.3 (9/109)	16.1 (15/93)	11.4 (21/185)	18.5 (17/92)	3.2 (3/93)
	Week 4	26.6 (29/109)	38.7 (43/111)	11.9 (13/109)	17.2 (16/93)	19.5 (36/185)	31.5 (29/92)	6.5 (6/93)
	Week 8	33.9 (37/109)	41.4 (46/111)	14.7 (16/109)	21.5 (20/93)	21.6 (40/185)	37.0 (34/92)	9.7 (9/93)
	Week 16 (♦)	43.1 (47/109)	47.7 (53/111)	22.9 (25/109)	22.6 (21/93)	27.6 (51/185)	31.5 (29/92)	17.2 (16/93)
	Week 32	—	45.1 (46/102)[a)]	—	25.8 (24/93)	25.4 (47/185)	25.0 (23/92)	18.3 (17/93)
	Week 52	—	34.3 (35/102)[a)]	—	22.6 (21/93)	20.0 (37/185)	25.0 (23/92)	20.4 (19/93)
Proportion of subjects achieving EASI50	Week 2	47.7 (52/109)	64.9 (72/111)	24.8 (27/109)	34.4 (32/93)	40.5 (75/185)	51.1 (47/92)	22.6 (21/93)
	Week 4	66.1 (72/109)	74.8 (83/111)	33.9 (37/109)	43.0 (40/93)	53.0 (98/185)	60.9 (56/92)	26.9 (25/93)
	Week 8	63.3 (69/109)	74.8 (83/111)	44.0 (48/109)	46.2 (43/93)	53.5 (99/185)	62.0 (57/92)	32.3 (30/93)
	Week 16	64.2 (70/109)	70.3 (78/111)	41.3 (45/109)	45.2 (42/93)	51.4 (95/185)	52.2 (48/92)	35.5 (33/93)
	Week 32	—	63.7 (65/102)[a)]	—	39.8 (37/93)	43.8 (81/185)	40.2 (37/92)	28.0 (26/93)
	Week 52	—	54.9 (56/102)[a)]	—	37.6 (35/93)	35.1 (65/185)	32.6 (30/92)	25.8 (24/93)
Proportion of subjects achieving EASI90	Week 2	4.6 (5/109)	6.3 (7/111)	4.6 (5/109)	7.5 (7/93)	3.2 (6/185)	5.4 (5/92)	0 (0/93)
	Week 4	10.1 (11/109)	16.2 (18/111)	5.5 (6/109)	4.3 (4/93)	4.3 (8/185)	13.0 (12/92)	1.1 (1/93)
	Week 8	15.6 (17/109)	18.0 (20/111)	4.6 (5/109)	6.5 (6/93)	5.4 (10/185)	15.2 (14/92)	3.2 (3/93)
	Week 16	16.5 (18/109)	24.3 (27/111)	13.8 (15/109)	8.6 (8/93)	10.3 (19/185)	14.1 (13/92)	6.5 (6/93)
	Week 32	—	21.6 (22/102)[a)]	—	14.0 (13/93)	10.8 (20/185)	14.1 (13/92)	10.8 (10/93)
	Week 52	—	17.6 (18/102)[a)]	—	14.0 (13/93)	9.7 (18/185)	14.1 (13/92)	11.8 (11/93)
Proportion of subjects achieving itch NRS ≥4	Week 2	23.7 (23/97)	33.0 (33/100)	15.4 (16/104)	14.1 (11/78)	13.9 (23/166)	22.4 (17/76)	4.7 (4/85)
	Week 4	34.0 (33/97)	52.0 (52/100)	10.6 (11/104)	19.2 (15/78)	24.1 (40/166)	40.8 (31/76)	8.2 (7/85)
	Week 8	30.9 (30/97)	47.0 (47/100)	15.4 (16/104)	17.9 (14/78)	23.5 (39/166)	42.1 (32/76)	8.2 (7/85)
	Week 16	38.1 (37/97)	44.0 (44/100)	20.2 (21/104)	23.1 (18/78)	22.9 (38/166)	38.2 (29/76)	8.2 (7/85)
	Week 32	—	40.7 (37/91)[a)]	—	20.5 (16/78)	16.3 (27/166)	22.1 (17/77)	12.9 (11/85)
	Week 52	—	—	—	23.1 (18/78)	12.0 (20/166)	16.9 (13/77)	12.9 (11/85)

% (n/N); ♦, primary endpoint of BREEZE-AD7 and -AD4; *, primary endpoint of BREEZE-AD7; —, no data
a) Data from subjects who entered the BREEZE-AD3 study after completion of the BREEZE-AD7 study (data at Weeks 16 and 36 in the BREEZE-AD3 study)

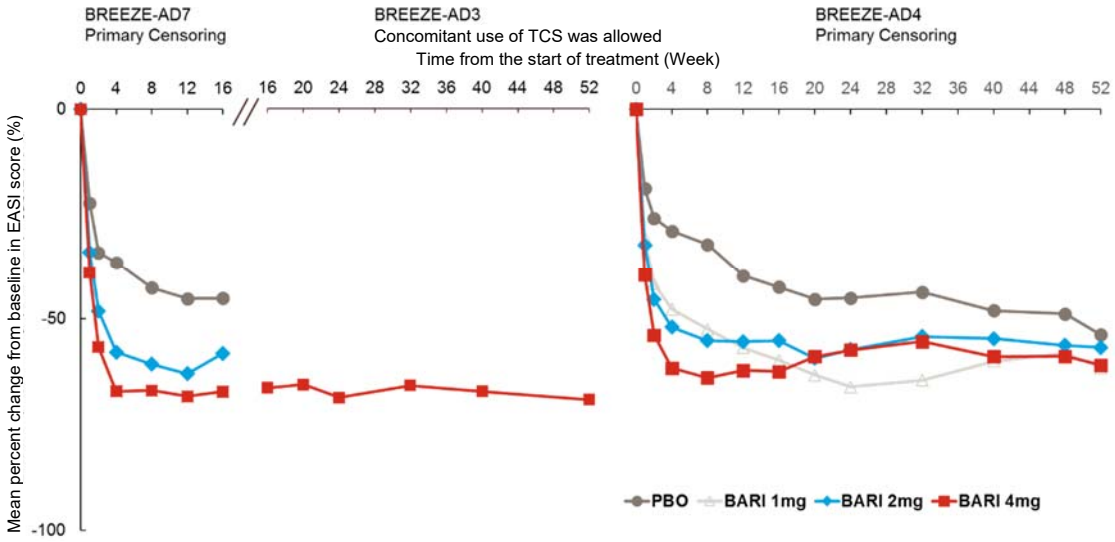


Figure 4. Least square mean percent change from baseline in EASI score (overall study population, mixed-effect model of repeated measure [MMRM])

Left = BREEZE-AD7 (including data after enrolling in BREEZE-AD3); Right = BREEZE-AD4

Table 21 and Figure 5 show the outcomes of key efficacy endpoints in the Japanese subpopulation in the BREEZE-AD7 and BREEZE-AD4 studies. In the BREEZE-AD7 study, unlike the trends in the overall study

group, the data of the 4 mg group are similar to those of the placebo group for the endpoints measuring the proportion of subjects achieving the goals; in contrast, the results of the 2 mg group and percent change from baseline in EASI score tended to be similar to those of the overall study population. In the BREEZE-AD4 study, outcomes for the Japanese subpopulation tended to be similar to those for the overall study population for all endpoints and at all the dose levels.

Table 21. Outcomes of key efficacy endpoints in studies evaluating baricitinib in combination with TCS (ITT population, NRI, Japanese subpopulation)

	Time point	BREEZE-AD7			BREEZE-AD4			
		2 mg	4 mg	Placebo	1 mg	2 mg	4 mg	Placebo
Proportion of subjects achieving IGA 0 or 1	Week 2	0 (0/20)	9.1 (2/22)	4.8 (1/21)	6.3 (1/16)	0 (0/32)	12.5 (2/16)	0 (0/15)
	Week 4	10.0 (2/20)	13.6 (3/22)	0 (0/21)	6.3 (1/16)	9.4 (3/32)	18.8 (3/16)	0 (0/15)
	Week 8	15.0 (3/20)	9.1 (2/22)	0 (0/21)	6.3 (1/16)	9.4 (3/32)	12.5 (2/16)	0 (0/15)
	Week 16 (*)	15.0 (3/20)	9.1 (2/22)	9.5 (2/21)	12.5 (2/16)	18.8 (6/32)	18.8 (3/16)	0 (0/15)
	Week 32	—	11.8 (2/17)[a)]	—	12.5 (2/16)	6.3 (2/32)	12.5 (2/16)	13.3 (2/15)
	Week 52	—	11.8 (2/17)[a)]	—	0 (0/16)	3.1 (1/32)	18.8 (3/16)	13.3 (2/15)
Proportion of subjects achieving EASI75	Week 2	20.0 (4/20)	22.7 (5/22)	9.5 (2/21)	31.3 (5/16)	12.5 (4/32)	43.8 (7/16)	0 (0/15)
	Week 4	25.0 (5/20)	22.7 (5/22)	4.8 (1/21)	18.8 (3/16)	28.1 (9/32)	37.5 (6/16)	0 (0/15)
	Week 8	30.0 (6/20)	22.7 (5/22)	9.5 (2/21)	18.8 (3/16)	28.1 (9/32)	50.0 (8/16)	13.3 (2/15)
	Week 16 (♦)	55.0 (11/20)	22.7 (5/22)	19.0 (4/21)	18.8 (3/16)	31.3 (10/32)	43.8 (7/16)	6.7 (1/15)
	Week 32	—	35.3 (6/17)[a)]	—	25.0 (4/16)	34.4 (11/32)	31.3 (5/16)	20.0 (3/15)
	Week 52	—	17.6 (3/17)[a)]	—	18.8 (3/16)	12.5 (4/32)	18.8 (3/16)	13.3 (2/15)
Proportion of subjects achieving EASI50	Week 2	50.0 (10/20)	59.1 (13/22)	28.6 (6/21)	43.8 (7/16)	56.3 (18/32)	50.0 (8/16)	40.0 (6/15)
	Week 4	80.0 (16/20)	54.5 (12/22)	38.1 (8/21)	50.0 (8/16)	68.8 (22/32)	50.0 (8/16)	33.3 (5/15)
	Week 8	70.0 (14/20)	54.5 (12/22)	42.9 (9/21)	50.0 (8/16)	62.5 (20/32)	56.3 (9/16)	26.7 (4/15)
	Week 16	65.0 (13/20)	40.9 (9/22)	33.3 (7/21)	43.8 (7/16)	59.4 (19/32)	43.8 (7/16)	26.7 (4/15)
	Week 32	—	58.8 (10/17)[a)]	—	37.5 (6/16)	59.4 (19/32)	37.5 (6/16)	26.7 (4/15)
	Week 52	—	52.9 (9/17)[a)]	—	31.3 (5/16)	37.5 (12/32)	18.8 (3/16)	13.3 (2/15)
Proportion of subjects achieving EASI90	Week 2	5.0 (1/20)	4.5 (1/22)	9.5 (2/21)	12.5 (2/16)	3.1 (1/32)	12.5 (2/16)	0 (0/15)
	Week 4	10.0 (2/20)	9.1 (2/22)	4.8 (1/21)	12.5 (2/16)	9.4 (3/32)	25.0 (4/16)	0 (0/15)
	Week 8	10.0 (2/20)	4.5 (1/22)	4.8 (1/21)	12.5 (2/16)	6.3 (2/32)	12.5 (2/16)	0 (0/15)
	Week 16	15.0 (3/20)	9.1 (2/22)	14.3 (3/21)	12.5 (2/16)	15.6 (5/32)	25.0 (4/16)	0 (0/15)
	Week 32	—	5.9 (1/17)[a)]	—	12.5 (2/16)	3.1 (1/32)	18.8 (3/16)	13.3 (2/15)
	Week 52	—	5.9 (1/17)[a)]	—	6.3 (1/16)	3.1 (1/32)	12.5 (2/16)	13.3 (2/15)
Proportion of subjects achieving itch NRS ≥4	Week 2	22.2 (4/18)	35.0 (7/20)	14.3 (3/21)	20.0 (3/15)	21.4 (6/28)	25.0 (3/12)	0 (0/14)
	Week 4	33.3 (6/18)	40.0 (8/20)	0 (0/21)	20.0 (3/15)	35.7 (10/28)	25.0 (3/12)	0 (0/14)
	Week 8	22.2 (4/18)	35.0 (7/20)	4.8 (1/21)	20.0 (3/15)	32.1 (9/28)	25.0 (3/12)	0 (0/14)
	Week 16	33.3 (6/18)	15.0 (3/20)	4.8 (1/21)	13.3 (2/15)	25.0 (7/28)	25.0 (3/12)	0 (0/14)
	Week 32	—	13.3 (2/15)[a)]	—	13.3 (2/15)	28.6 (8/28)	8.3 (1/12)	14.3 (2/14)
	Week 52	—	—	—	20.0 (3/15)	14.3 (4/28)	8.3 (1/12)	7.1 (1/14)

% (n/N); ♦, primary endpoint of BREEZE-AD7 and BREEZE-AD4; *, primary endpoint of BREEZE-AD7; —, no data
a) Data from subjects who entered the BREEZE-AD3 study after completion of theBREEZE-AD7 study (data at Weeks 16 and 36 in the BREEZE-AD3 study)

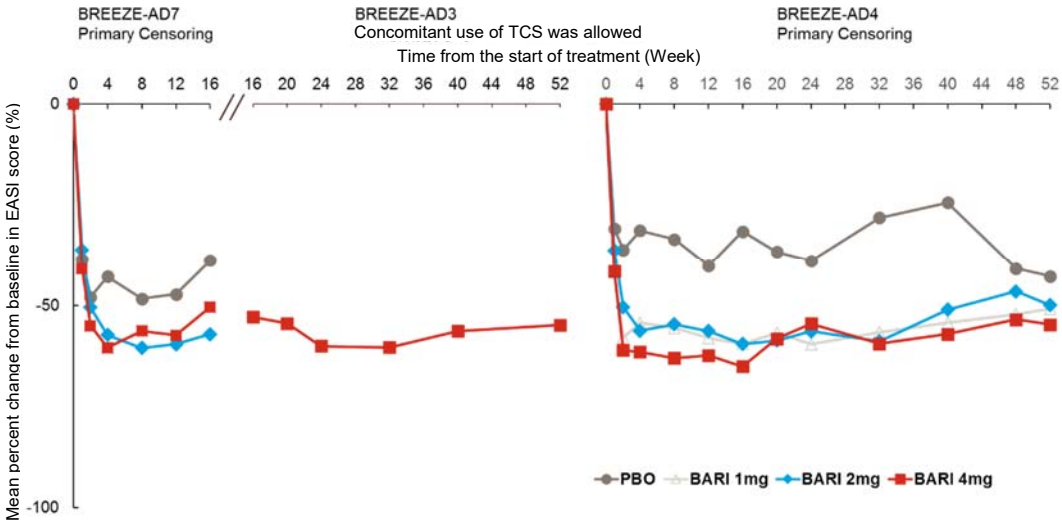


Figure 5. Least square mean percent change from baseline in EASI score (Japanese subpopulation, MMRM)
Left = BREEZE-AD7 (including data after enrolling in BREEZE-AD3); Right = BREEZE-AD4

The applicant's discussion on the causes for different trends between the data of the 4 mg group for the overall study population and the data of the 4 mg group for the Japanese subpopulation in the BREEZE-AD7 study:
Only approximately 20 subjects per group composed the Japanese subpopulation. This could be the reason for the discrepancy between the Japanese subpopulation and the overall study population in the BREEZE-AD7 study. In addition, as shown in Table 22, other factors such as the following may have affected the outcomes: the baseline BSA affected in the Japanese subpopulation was larger than that in the overall study population; and the amount of TCS used varied greatly among treatment groups.

Table 22. Baseline disease activity and use of TCS in subjects in the BREEZE-AD7 study (ITT population)

	Overall study population			Japanese subpopulation		
	2 mg (N = 109)	4 mg (N = 111)	Placebo (N = 109)	2 mg (N = 20)	4 mg (N = 22)	Placebo (N = 21)
Baseline disease activity						
Proportion of subjects with IGA of 4	45.9 (50/109)	45.0 (50/111)	44.4 (48/108)	45.0 (9/20)	40.9 (9/22)	42.9 (9/21)
EASI score	29.3 ± 11.9	30.9 ± 12.6	28.5 ± 12.3	30.8 ± 9.8	33.8 ± 11.3	37.1 ± 14.9
BSA affected	50.6 ± 21.6	52.1 ± 23.3	48.1 ± 24.4	59.7 ± 18.5	62.8 ± 19.2	67.8 ± 18.7
Use of moderate potency TCS as supplied by the sponsor up to Week 16 (g)						
TCS used	162 ± 166	137 ± 132	225 ± 258	266 ± 218	158 ± 120	406 ± 359

% (n/N) or mean ± standard deviation

The applicant's explanation about the efficacy of baricitinib in patients who were responders or partial responders on treatment with baricitinib:
In the BREEZE-AD3 study, subjects who were responders or partial responders on baricitinib 4 mg or 2 mg in Part 1 entered the withdrawal and down-titration substudy to be re-randomized in a blinded manner to continuation of the dose assigned in Part 2, the next lower dose (4 mg → 2 mg or 2 mg → 1 mg), or placebo (withdrawal) [see Section 7.2.5]. Subjects were to be re-treated with the dose assigned before entry in the substudy if their AD symptoms worsened to an IGA score of ≥3.

Table 23 shows the substudy results. Subjects who continued on baricitinib 4 mg or 2 mg without changing the dose assigned before entry in the substudy achieved outcomes similar to those at entry in the substudy. In contrast, decreases in the proportion of subjects achieving IGA 0 or 1 and in the proportion of subjects achieving EASI75 were observed in subjects withdrawn from baricitinib (placebo group) at 4 weeks after withdrawal. Subjects who underwent down-titration achieved outcomes almost similar to those at entry in the substudy, except for the trend toward a decrease in the proportion of subjects achieving EASI75 in subjects undergoing down-titration from 4 mg to 2 mg. The results suggest that the effect of baricitinib is maintained in a certain number of patients after dose reduction. In the majority of the subjects who experienced worsening of AD (to an IGA score of ≥3) after undergoing down-titration or withdrawal of baricitinib, retreatment on the pre-substudy dose level improved symptoms to achieve an IGA score of ≤2 (criteria for enrollment in the substudy), indicating a return of efficacy.

Table 23. Efficacy results in the BREEZE-AD3 substudy (mITT population, NRI)

	Substudy time point	Subjects receiving 4 mg in Part 1			Subjects receiving 2 mg in Part 1		
		4 mg (Extended)	2 mg (Down-titration)	Placebo (Withdrawal)	2 mg (Extended)	1 mg (Down-titration)	Placebo (Withdrawal)
Proportion of subjects achieving IGA 0 or 1	Entry	50.0 (34/68)	49.3 (34/69)	50.0 (34/68)	54.0 (34/63)	54.7 (35/64)	54.7 (35/64)
	Week 4	44.8 (30/67)	39.7 (27/68)	20.9 (14/67)	52.5 (31/59)	45.9 (28/61)	29.0 (18/62)
	Week 8	44.8 (30/67)	42.6 (29/68)	28.4 (19/67)	48.1 (26/54)	42.1 (24/57)	29.8 (17/57)
	Week 12	44.8 (30/67)	41.2 (28/68)	28.4 (19/67)	38.9 (21/54)	45.5 (25/55)	32.7 (18/55)
	Week 16	44.8 (30/67)	44.1 (30/68)	25.4 (17/67)	40.7 (22/54)	42.6 (23/54)	29.6 (16/54)
Proportion of subjects achieving EASI75	Entry	82.4 (56/68)	82.6 (57/69)	77.9 (53/68)	82.5 (52/63)	78.1 (50/64)	85.9 (55/64)
	Week 4	71.6 (48/67)	63.2 (43/68)	46.3 (31/67)	67.8 (40/59)	65.6 (40/61)	45.2 (28/62)
	Week 8	71.6 (48/67)	58.8 (40/68)	41.8 (28/67)	70.4 (38/54)	63.2 (36/57)	45.6 (26/57)
	Week 12	76.1 (51/67)	48.5 (33/68)	40.3 (27/67)	68.5 (37/54)	65.5 (36/55)	47.3 (26/55)
	Week 16	73.1 (49/67)	47.1 (32/68)	32.8 (22/67)	66.7 (36/54)	68.5 (37/54)	38.9 (21/54)
		Proportion of subjects achieving each efficacy endpoint within 16 weeks of retreatment on the Part-1 dose level due to worsening of AD					
		4 mg to 4 mg	2mg to 4 mg	Placebo to 4mg	2 mg to 2 mg	1 mg to 2 mg	Placebo to 2mg
Proportion of subjects achieving IGA 0, 1, or 2		64.7 (11/17)	86.2 (25/29)	86.5 (32/37)	80.0 (16/20)	62.5 (10/16)	90.0 (27/30)
Proportion of subjects achieving IGA 0 or 1		17.6 (3/17)	27.6 (8/29)	48.6 (18/37)	5.0 (1/20)	37.5 (6/16)	50.0 (15/30)
Proportion of subjects achieving EASI75		64.7 (11/17)	58.6 (17/29)	75.7 (28/37)	65.0 (13/20)	50.0 (8/16)	70.0 (21/30)

% (n/N)

The above results demonstrate that the efficacy of baricitinib 4 mg in patients with AD, and baricitinib 2 mg can also be expected to be effective.

PMDA's view:

The results of the BREEZE-AD7 and BREEZE-AD4 studies, which evaluated baricitinib in combination with TCS, demonstrated the superiority of baricitinib 4 mg over placebo. In addition, the outcomes of other efficacy endpoints support the efficacy of baricitinib 4 mg, suggesting that baricitinib 4 mg is effective in the treatment of AD. For some of the endpoints in the 4 mg group in the BREEZE-AD7 study, a trend in the Japanese subpopulation was inconsistent with that in the overall study population. The applicant's interpretation that the results may have been incidental due to reasons including the small sample size of the Japanese subpopulation is reasonable. The results for the Japanese subpopulation in the BREEZE-AD7 study suggest that baricitinib 4 mg is superior to placebo for several endpoints at most time points. Although some point estimates are lower than those of placebo, the difference is slight. Given that the results for the Japanese subpopulation in the

BREEZE-AD4 study are similar to those for the overall study population, baricitinib is expected to be effective in Japanese patients as well.

The BREEZE-AD7 and BREEZE-AD4 studies, which evaluated baricitinib in combination with TCS, failed to demonstrate the superiority of baricitinib 2 mg over placebo; however, the results for baricitinib 2 mg tended to be better than those for placebo for key efficacy endpoints, with a trend similar to the results for the Japanese subpopulation (Table 20 and Table 21, Figure 4 and Figure 5). The BREEZE-AD1 and BREEZE-AD2 studies, in which TCS was not used concomitantly, demonstrated the superiority of baricitinib 2 mg over placebo. The results from the clinical study, in which 2 mg was continuously administered or the dose was reduced from 4 mg to 2 mg in the long-term treatment described below, are also expected to demonstrate the efficacy of baricitinib 2 mg to a certain extent.

The long-term efficacy of baricitinib was evaluated in the substudy in the BREEZE-AD3 study, in which decreases in the proportion of subjects achieving IGA 0 or 1 and in the proportion of subjects achieving EASI75 were observed in subjects withdrawn from baricitinib (placebo group) at 4 weeks after withdrawal. In contrast, subjects who continued on baricitinib 4 mg or 2 mg achieved a response similar to the response at entry in the substudy while subjects who received 4 mg prior to treatment with the 2 mg dose in the substudy were able to maintain a certain level of response at the reduced dose (Table 23). Based on the results, continued treatment with baricitinib 4 mg or 2 mg is expected to be effective in patients with AD who achieved a certain level of efficacy with baricitinib. In addition, the effects of baricitinib are expected to be maintained even after dose reduction to the 2 mg dose in some patients with AD achieving a certain level of efficacy with baricitinib 4 mg.

The PMDA's conclusion above will be discussed at the Expert Discussion.

7.R.3 Safety

7.R.3.1 Safety summary

The applicant's explanation about the safety of baricitinib in patients with AD based on the results of pooled populations from clinical studies in Japan and other countries as shown in Table 24.

Table 24. Definition of pooled populations used for safety evaluation

Name of pooled population data	Patient population	Studies (data cut-off date)
Pooled data from 2 monotherapy studies	AD	BREEZE-AD1 and BREEZE-AD2
Pooled data from 3 TCS combination studies		I4V-MC-JAHG, BREEZE-AD4, and BREEZE-AD7
Pooled data from 6 studies in Japan and overseas		I4V-MC-JAHG, BREEZE-AD1, BREEZE-AD2, and BREEZE-AD7 BREEZE-AD3 ([redacted], 2020), BREEZE-AD4 ([redacted], 2020)
Pooled data from 10 studies in Japan and overseas	RA	JADA/JADY, JADB, JADC, JADN, JAGS/JADY, JADV/JADY, JADW/JADY, JADX/JADY, and JADZ/JADY ([redacted], 2018)

Table 25 summarizes the safety of baricitinib in each pooled population data set. Table 26 shows the incidence of adverse events that may be associated with the use of baricitinib. With the exception of herpes simplex virus

infections [see Section 7.R.3.2 for skin infections], data show no clear differences in the safety profile of baricitinib between patients with AD and patients with RA, the approved indication of baricitinib.

Table 25 shows the safety summary of baricitinib in Japanese patients with AD.
Table 27 shows the incidence of adverse events that may be associated with the use of baricitinib in Japanese patients with AD. Data show no clear differences in the safety profile of baricitinib between Japanese patients with AD and the overall study population.

Table 25. Safety summary of baricitinib (safety analysis set)

	Patients with AD							Patients with RA
	Pooled data from 2 monotherapy studies			Pooled data from 3 TCS combination studies			Pooled data from 6 studies in Japan and overseas	Pooled data from 10 studies in Japan and overseas
	2 mg	4 mg	Placebo	2 mg	4 mg	Placebo	Baricitinib-treated subjects	Baricitinib-treated subjects
Overall study population								
N	246	248	493	330	241	250	2,157	3,770
Total exposure (person-years)	72.2	75.5	142.9	96.9	71.6	68.9	2,364.4	10,127
All adverse events	142 (57.7) 196.7	139 (56.0) 184.1	272 (55.2) 190.3	205 (62.1) 211.6	161 (66.8) 224.9	116 (46.4) 168.4	1,599 (74.1) 67.6	3,332 (88.4) 32.9
Serious adverse events	3 (1.2) 4.2	3 (1.2) 4.0	15 (3.0) 10.5	7 (2.1) 7.2	11 (4.6) 15.4	6 (2.4) 8.7	141 (6.5) 6.0	849 (22.5) 8.2[a)]
Adverse events leading to treatment discontinuation	4 (1.6) 5.5	3 (1.2) 4.0	6 (1.2) 4.2	6 (1.8) 6.2	12 (5.0) 16.8	7 (2.8) 10.2	96 (4.5) 4.1	518 (13.7) 5.0[a)]
Adverse reactions	42 (17.1) 58.2	55 (22.2) 72.8	61 (12.4) 42.7	80 (24.2) 82.6	57 (23.7) 79.6	45 (18.0) 65.3	626 (29.0) 26.5	1,935 (51.3) 19.1
Deaths	0 0	0 0	0 0	0 0	0 0	0 0	1 (0.05) 0.04	44 (1.2) 0.43
Japanese subpopulation								
N	43	45	90	58	44	44	341	514
Total exposure (person-years)	12.8	13.7	26.0	17.9	13.1	13.1	441.1	1,240.0
All adverse events	28 (65.1) 218.8	24 (53.3) 175.2	49 (54.4) 188.5	23 (39.7) 128.5	28 (63.6) 213.7	14 (31.8) 106.9	257 (75.4) 58.3	501 (97.5) 40.4
Serious adverse events	0 0	1 (2.2) 7.3	3 (3.3) 11.5	0 0	2 (4.5) 15.3	0 0	18 (5.3) 4.1	102 (19.8) 8.0[a)]
Adverse events leading to treatment discontinuation	1 (2.3) 7.8	1 (2.2) 7.3	0 0	1 (1.7) 5.6	4 (9.1) 30.5	0 0	19 (5.6) 4.3	96 (18.7) 7.6[a)]
Adverse reactions	5 (11.6) 39.1	12 (26.7) 87.6	12 (13.3) 46.2	5 (8.6) 27.9	6 (13.6) 45.8	2 (4.5) 15.3	98 (28.7) 22.2	411 (80.0) 33.1
Deaths	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0

Upper row, n (%); lower row, events per 100 person-years adjusted for total exposure time
Pooled data analyses in patients with AD include follow-up period.
a) Calculated based on the exposure time including the follow-up period (10,301 person-years for the overall study population and 1,269.5 person-years for the Japanese subpopulation)

Table 26. Incidence of adverse events that may be associated with baricitinib (safety analysis set)

	Patients with AD							Patients with RA
	Pooled data from 2 monotherapy studies			Pooled data from 3 TCS combination studies			Pooled data from 6 studies in Japan and overseas	Pooled data from 10 studies in Japan and overseas
	2 mg	4 mg	Placebo	2 mg	4 mg	Placebo	Baricitinib-treated subjects	Baricitinib-treated subjects
N	246[a)]	248[b)]	493[c)]	330[d)]	241[e)]	250[f)]	2,157[g)]	3,770[h)]
Total exposure (person-years)	72.2	75.5	142.9	96.9	71.6	68.9	2,364.4	10,127
Infections	84 (34.1) 116.3	84 (33.9) 111.3	150 (30.4) 105.0	128 (38.8) 132.1	99 (41.1) 138.3	66 (26.4) 95.8	1,206 (55.9) 51.0	2,409 (63.9) 23.8
Serious infections	0 0	1 (0.4) 1.3	2 (0.4) 1.4	3 (0.9) 3.1	2 (0.8) 2.8	3 (1.2) 4.4	51 (2.4) 2.2	259 (6.9) 2.6
Opportunistic infections	0 0	0 0	0 0	1 (0.3) 1.0	0 0	1 (0.4) 1.5	7 (0.3) 0.3	52 (1.4) 0.5[i)]
Active tuberculosis	0 0	0 0	0 0	0 0	0 0	0 0	0 0	15 (0.4) 0.1[i)]
Herpes zoster	2 (0.8) 2.8	0 0	1 (0.2) 0.7	4 (1.2) 4.1	0 0	2 (0.8) 2.9	61 (2.8) 2.6	319 (8.5) 3.1
Hepatitis B	0 0	0 0	0 0	0 0	0 0	0 0	1 (0.05) 0.04	10 (0.3) 0.1
NMSC	0 0	0 0	0 0	0 0	0 0	1 (0.4) 1.5	6 (0.3) 0.3	37 (1.0) 0.4[i)]
Malignancies (excluding NMSC)	0 0	0 0	2 (0.4) 1.4	0 0	0 0	0 0	3 (0.1) 0.1	85 (2.3) 0.8
Lymphoma	0 0	0 0	0 0	0 0	0 0	0 0	2 (0.1) 0.1	8 (0.2) 0.1
Gastrointestinal perforation	0 0	0 0	0 0	0 0	0 0	0 0	2 (0.1) 0.1	4 (0.1) 0.04[i)]
Interstitial lung disease	0 0	0 0	0 0	0 0	0 0	0 0	0 0	15 (0.4) 0.1
Dyslipidaemia	5 (2.0) 6.9	5 (2.0) 6.6	6 (1.2) 4.2	9 (2.7) 9.3	2 (0.8) 2.8	3 (1.2) 4.4	65 (3.0) 2.7	623 (16.5) 6.2
MACE	0 0	0 0	0 0	0 0	0 0	0 0	2 (0.1) 0.1	51 (1.6)[i)] 0.5[i)]
Venous thromboembolism	0 0	0 0	0 0	0 0	1 (0.4) 1.4	0 0	3 (0.1) 0.1	49 (1.3) 0.5[i)]
Anaemia	0 0	0 0	0 0	0 0	0 0	0 0	0 0	31 (0.8) 0.3
Decreased neutrophils	0 0	0 0	0 0	1 (0.3) 1.0	1 (0.4) 1.4	0 0	7 (0.3) 0.3	36 (1.0) 0.4
Decreased lymphocytes	0 0	0 0	0 0	0 0	3 (1.3) 4.2	1 (0.4) 1.5	13 (0.6) 0.5	144 (3.9) 1.4
Platelet count increased	4 (1.6) 5.5	1 (0.4) 1.3	0 0	3 (0.9) 3.1	2 (0.8) 2.8	0 0	26 (1.2) 1.1	127 (3.4) 1.3
Pancytopenia	0 0	0 0	0 0	0 0	0 0	0 0	0 0	4 (0.1) 0.04
CPK increased	6 (2.5) 8.3	9 (3.6) 11.9	9 (1.9) 6.3	8 (2.5) 8.3	7 (2.9) 9.8	5 (2.1) 7.3	93 (4.4) 3.9	111 (3.1) 1.1
Rhabdomyolysis/myopathy	0 0	3 (1.2) 4.0	1 (0.2) 0.7	3 (0.9) 3.1	0 0	2 (0.8) 2.9	27 (1.3) 1.1	174 (4.6) 1.7
ALP increased	1 (0.4) 1.4	0 0	1 (0.2) 0.7	1 (0.3) 1.0	0 0	1 (0.4) 1.5	8 (0.4) 0.3	225 (6.0) 2.2
ALT increased	1 (0.4) 1.4	1 (0.4) 1.3	5 (1.0) 3.5	2 (0.6) 2.1	0 0	2 (0.8) 2.9	39 (1.8) 1.6	161 (4.3) 1.6
AST increased	1 (0.4) 1.4	2 (0.8) 2.6	5 (1.0) 3.5	4 (1.2) 4.1	1 (0.4) 1.4	2 (0.8) 2.9	41 (1.9) 1.7	93 (2.5) 0.9
Total bilirubin increased	0 0	1 (0.4) 1.3	3 (0.6) 2.1	1 (0.3) 1.0	0 0	0 0	10 (0.5) 0.4	3 (0.1) 0.03
Serum creatinine increased	0 0	0 0	0 0	0 0	0 0	1 (0.4) 1.5	1 (0.05) 0.04	4 (0.1) 0.04
Depression or suicidal/self-injurious behavior	1 (0.4) 1.4	5 (2.0) 6.6	7 (1.4) 4.9	6 (1.0) 6.2	7 (1.4) 9.8	8 (1.1) 11.6	32 (1.5) 1.4	134 (3.6) 1.3

Upper row, n (%); lower row, events per 100 person-years adjusted for total exposure time
Pooled data analyses in patients with AD include follow-up period.
See Section 10 for the definitions of events and footnotes.

Table 27. Incidence of adverse events that may be associated with baricitinib (safety analysis set, Japanese subpopulation)

	Patients with AD							Patients with RA
	Pooled data from 2 monotherapy studies			Pooled data from 3 TCS combination studies			Pooled data from 6 studies in Japan and overseas	Pooled data from 10 studies in Japan and overseas
	2 mg	4 mg	Placebo	2 mg	4 mg	Placebo	Baricitinib-treated subjects	Baricitinib-treated subjects
N	43	45	90	58	44	44[a)]	341[b)]	514[c)]
Total exposure (person-years)	12.8	13.7	26.0	17.9	13.1	13.1	441.1	1,240.0
Infections	18 (41.9) 140.7	18 (40.0) 131.1	25 (27.8) 96.0	17 (29.3) 95.0	17 (38.6) 129.8	9 (20.5) 68.7	198 (58.1) 44.9	396 (77.0) 31.9
Serious infections	0 0	1 (2.2) 7.3	0 0	0 0	0 0	0 0	8 (2.3) 1.8	34 (6.6) 2.7
Opportunistic infections	0 0	0 0	0 0	0 0	0 0	0 0	1 (0.3) 0.2	24 (4.7) 1.9[d)]
Active tuberculosis	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0[d)]
Herpes zoster	1 (2.3) 7.8	0 0	0 0	0 0	0 0	0 0	12 (3.5) 2.7	80 (15.6) 6.5
Hepatitis B	0 0	0 0	0 0	0 0	0 0	0 0	0 0	3 (0.6) 0.2
NMSC	0 0	0 0	0 0	0 0	0 0	0 0	0 0	1 (0.2) 0.08[d)]
Malignancies (excluding NMSC)	0 0	0 0	0 0	0 0	0 0	0 0	2 (2.6) 0.5	14 (2.7) 1.1
Lymphoma	0 0	0 0	0 0	0 0	0 0	0 0	1 (0.3) 0.2	3 (0.6) 0.2
Gastrointestinal perforation	0 0	0 0	0 0	0 0	0 0	0 0	0 0	1 (0.2) 0.08[d)]
Interstitial lung disease	0 0	0 0	0 0	0 0	0 0	0 0	0 0	5 (1.0) 0.4
Dyslipidaemia	0 0	1 (2.2) 7.3	0 0	2 (3.4) 11.2	1 (2.3) 7.6	1 (2.3) 7.6	11 (3.2) 2.5	116 (22.6) 9.4
MACE	0 0	0 0	0 0	0 0	0 0	0 0	1 (0.3) 0.2	4 (1.1)[e)] 0.4[d)]
Venous thromboembolism	0 0	0 0	0 0	0 0	0 0	0 0	0 0	4 (0.8) 0.3[d)]
Anaemia	0 0	0 0	0 0	0 0	0 0	0 0	0 0	4 (0.8) 0.3
Decreased neutrophils	0 0	0 0	0 0	0 0	0 0	0 0	1 (0.3) 0.2	4 (0.8) 0.3
Decreased lymphocytes	0 0	0 0	0 0	0 0	2 (4.5) 15.3	0 0	2 (0.6) 0.5	49 (9.5) 4.0
Platelet count increased	1 (2.3) 7.8	0 0	0 0	1 (1.7) 5.6	0 0	0 0	7 (2.1) 1.6	14 (2.7) 1.1
Pancytopenia	0 0	0 0	0 0	0 0	0 0	0 0	0 0	1 (0.2) 0.1
CPK increased	0 0	1 (2.2) 7.3	1 (1.1) 3.8	1 (1.7) 5.6	1 (2.3) 7.6	1 (2.3) 7.6	13 (3.8) 2.9	19 (3.7) 1.5
Rhabdomyolysis/myopathy	0 0	0 0	0 0	0 0	0 0	0 0	3 (0.9) 0.7	24 (4.7) 1.9
ALP increased	0 0	0 0	0 0	0 0	0 0	0 0	0 0	18 (3.5) 1.5
ALT increased	0 0	0 0	0 0	0 0	0 0	0 0	6 (1.8) 1.4	39 (7.6) 3.1
AST increased	0 0	0 0	0 0	1 (1.7) 5.6	0 0	0 0	8 (2.4) 1.8	18 (3.5) 1.5
Total bilirubin increased	0 0	0 0	0 0	0 0	0 0	0 0	1 (0.3) 0.2	0 0
Serum creatinine increased	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
Depression or suicidal/self-injurious behavior	0 0	0 0	0 0	0 0	0 0	0 0	1 (0.3) 0.2	4 (0.8) 0.3

Upper row, n (%); lower row, events per 100 person-years adjusted for total exposure time
Pooled data analyses in patients with AD include follow-up period.
See Section 10 for the definitions of events and footnotes.

According to the post-marketing safety information on bariticinib, venous thromboembolism was reported in patients who received baricitinib, and a causal relationship between baricitinib and the event could not be ruled out. For this reason, "venous thromboembolism" was included in the "Clinically Significant Adverse Reactions" section of the package insert, and its classification was changed from "important potential risk" to "important identified risk." As of February 13, 2020, the post-marketing data obtained in Japan and overseas showed no new safety concerns. The data include those from the specified use-results survey in patients with RA (of 4,806 patients registered, 2,016 patients submitted questionnaires on their status at 24 weeks of treatment) and from the post-marketing clinical study (including 268 Japanese subjects). No findings have suggested the need for revisions of the established risk profiles of baricitinib, including serious infections (such as herpes zoster and pneumonia), hepatotoxicity, and teratogenicity.

On the basis of the above, the applicant considers that risks for adverse events associated with the use of baricitinib in patients with AD can be managed well by implementing safety measures, as with those currently in place for the approved indication.

PMDA's view:
The submitted clinical study results and post-marketing safety information in Japan and overseas have raised no new safety concerns specific to patients with AD compared to the safety profile of baricitinib in the approved RA indication, except for skin infections discussed below, although the variation in factors such as patient characteristics, exposure time, and concomitant treatments precludes a direct comparison between studies. Therefore, the applicant should take safety measures that are the same as those currently in place for the approved indication (the treatment of RA).

The PMDA's conclusion above will be discussed at the Expert Discussion.

7.R.3.2 Skin infections

The applicant's explanation about skin infection-related adverse events[17)] associated with the use of baricitinib in patients with AD:
Table 28 shows the incidence of skin infections and herpes zoster in each pooled analysis population. There were no clear differences in the incidence of fungal skin infection and herpes zoster between patients with AD and those with RA. In the pooled data from 2 monotherapy studies and pooled data from 3 TCS combination studies, the incidence of bacterial skin infections in the baricitinib groups was similar to that in the placebo group. On the other hand, herpes simplex virus infections were reported more frequently in patients with AD than in patients with RA. In the pooled data from 2 monotherapy studies and pooled data from 3 TCS combination studies, the incidence of herpes simplex virus infections was higher in the baricitinib group (especially at 4 mg), compared to placebo.

[17)] In this section, skin infections include "bacterial skin infections," "fungal skin infections," or "herpes simplex virus infections."

Table 29 shows the incidence of skin infections in baricitinib-treated subjects by treatment period in the pooled data from 6 studies in Japan and overseas. Skin infections occurred frequently during the early stage of treatment, and then decreased in Month 3 and thereafter, suggesting that the risk of developing skin infections did not increase in a manner proportional to the duration of treatment.

In the pooled data from 6 studies in Japan and overseas, serious skin infections occurred in 13 subjects (eczema herpeticum in 11 subjects, furuncle in 1 subject, and staphylococcal infection in 1 subject). No deaths occurred. All events resolved (11 subjects) or were resolving (1 subject), except for 1 subject who discontinued treatment (outcome was reported as “resolved”).

The above findings suggest that herpes simplex virus infections are common among patients with AD (*Am J Clin Dermatol*. 2019;20:443-56). The events including serious ones can be treated with appropriate care. Therefore, herpes simplex virus infections can be managed with the current cautionary advice on infections, which includes the statement about infections in the “WARNINGS” section and the inclusion of herpes simplex in the “Other Adverse Reactions” section of the package insert.

Table 28. Incidence of skin infections and herpes zoster (safety analysis set)

	Patients with AD							Patients with RA
	Pooled data from 2 monotherapy studies			Pooled data from 3 TCS combination studies[d]			Pooled data from 6 studies in Japan and overseas[d]	Pooled data from 10 studies in Japan and overseas
	2 mg	4 mg	Placebo	2 mg	4 mg	Placebo	Baricitinib-treated subjects	Baricitinib-treated subjects
Overall study population								
N	246	248	493	330	241	250	2,157	3,770
Total exposure (person-years)	72.2	75.5	142.9	96.9	71.6	68.9	2,364.4	10,127
Skin bacterial infection[a]	15 (6.1) 20.8	10 (4.0) 13.2	30 (6.1) 21.0	16 (5.5) 18.5	8 (3.9) 13.1	8 (4.0) 14.1	64 (3.1) 2.7	_[e]
Of which, serious events	0 0	0 0	2 (0.4) 1.4	1 (0.3) 1.2	1 (0.5) 1.6	1 (0.5) 1.8	3 (0.1) 0.1	_[e]
Fungal skin infection[b]	4 (1.6) 5.5	0 0	1 (0.2) 0.7	1 (0.3) 1.0	4 (1.7) 5.6	0 0	41 (1.9) 1.7	155 (4.1) 1.5
Of which, serious events	0 0	0 0	0 0	0 0	0 0	0 0	0 0	1 (0.03) 0.01
Herpes simplex virus infection[c]	11 (4.5) 15.2	14 (5.6) 18.5	14 (2.8) 9.8	14 (4.2) 14.4	21 (8.7) 29.3	8 (3.2) 11.6	222 (10.3) 9.4	141 (3.7) 1.4
Of which, serious events	0 0	0 0	2 (0.4) 1.4	0 0	0 0	0 0	11 (0.5) 0.5	2 (0.1) 0.02
Herpes zoster	2 (0.8) 2.8	0 0	1 (0.2) 0.7	4 (1.2) 4.1	0 0	2 (0.8) 2.9	61 (2.8) 2.6	319 (8.5) 3.1
Of which, serious events	0 0	0 0	0 0	0 0	0 0	0 0	0 0	38 (1.0) 0.4
Japanese subpopulation								
N	43	45	90	58	44	44	341	514
Total exposure (person-years)	12.8	13.7	26.0	17.9	13.1	13.1	441.1	1,240.0
Skin bacterial infection[a]	1 (2.3) 7.8	2 (4.4) 14.6	5 (5.6) 19.2	5 (9.6) 31.1	1 (2.6) 8.8	3 (8.3) 27.8	13 (4.0) 3.0	_[e]
Of which, serious events	0 0	0 0	0 0	0 0	0 0	0 0	0 0	_[e]
Fungal skin infection[b]	1 (2.3) 7.8	0 0	1 (1.1) 3.8	1 (1.7) 5.6	0 0	0 0	10 (2.9) 2.3	33 (6.4) 2.7
Of which, serious events	0 0	0 0	0 0	0 0	0 0	0 0	0 0	1 (0.2) 0.1
Herpes simplex virus infection[c]	3 (7.0) 23.5	4 (8.9) 29.1	3 (3.3) 11.5	2 (3.4) 11.2	3 (6.8) 22.9	0 0	32 (9.4) 7.3	37 (7.2) 3.0
Of which, serious events	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
Herpes zoster	1 (2.3) 7.8	0 0	0 0	0 0	0 0	0 0	12 (3.5) 2.7	80 (15.6) 6.5
Of which, serious events	0 0	0 0	0 0	0 0	0 0	0 0	0 0	15 (2.9) 1.2

Upper row, n (%); lower row, events per 100 person-years adjusted for total exposure time
Pooled data analyses in patients with AD include follow-up period.
a) Skin infection requiring antibiotic treatment
b) High-level terms (HLTs) “Fungal infections NEC” and “Tinea infections”
c) Including oral herpes, Kaposi’s varicelliform eruption, eczema herpeticum, ophthalmic herpes simplex, and genital herpes
d) In Study JAHG, no detailed data on skin bacterial infections were collected, and therefore the data were not included in the analysis. The number of subjects reported and total exposure (person-years; PY) for each treatment group are as follows: In the overall study population: pooled data from 3 TCS combination studies, 293 subjects (86.6 PY) in the 2 mg group, 203 subjects (61.1 PY) in the 4 mg group, 201 subjects (56.7 PY) in the placebo group; pooled data from 6 studies in Japan and overseas: 2,082 subjects (2,343.7 PY). In the Japanese subpopulation: pooled data from 3 TCS combination studies, 52 subjects (16.1 PY) in the 2 mg group, 38 subjects (11.3 PY) in the 4 mg group, 36 subjects (10.8 PY) in the placebo group; pooled data from 6 studies in Japan and overseas, 329 subjects (437.5 PY).
e) No detailed data on skin bacterial infections were collected.

Table 29. Incidence of skin infections in baricitinib-treated subjects by treatment period in the pooled data from 6 studies in Japan and overseas.

	Month 0-3	Month 3-6	Month 6-9	Month 9-12	Month 12-15	Month 15-18	Month 18-21	From Month 21
N	2,157	2,014	1,744	1,552	1,329	799	621	456
Skin infections	150 (7.0)	98 (4.9)	55 (3.2)	35 (2.3)	32 (2.4)	27 (3.4)	10 (1.6)	8 (1.8)

n (%)

PMDA's view:

AD is often complicated by bacterial, fungal, or viral infections due to decreased skin barrier functions and decreased skin immune activity (Clinical Practice Guidelines for the Management of Atopic Dermatitis 2018 [in Japanese]. *Jpn J Dermatol.* 2018;128:2431-2502). In clinical studies of baricitinib, the incidence and exposure-adjusted incidence of herpes simplex virus infections were higher in patients with AD than in patients with RA. Herpes virus simplex infections occurred in a dose proportional manner, and serious skin infections also occurred in a certain number of patients. In addition, baricitinib has immunosuppressive effects. Given these facts, patients should be closely monitored for skin infections during treatment with baricitinib. Based on the above, healthcare professionals should be advised to be aware of the risk of skin infections in patients with AD during treatment with baricitinib, in addition to the cautionary statements for infections in the current package insert.

The PMDA's conclusion above will be discussed at the Expert Discussion.

7.R.4 Clinical positioning and indications

7.R.4.1 Indications

The applicant's explanation:

At the regulatory submission of the present application, the proposed indication of baricitinib was "moderate to severe atopic dermatitis"; however, based on the patient population and results from the clinical studies, as well as the expected clinical positioning of baricitinib for the treatment of AD [see Section 7.R.4.2], the indication for the present application was re-examined and modified to "atopic dermatitis in patients who have had an inadequate response to conventional treatments." The following cautionary statement was added to the "Precautions Concerning Indication" section of the package insert: "Baricitinib should be used in patients who, after a reasonable duration of treatment, had an inadequate response to appropriate treatment with topical anti-inflammatory drugs, such as TCS and TCI."

PMDA's view:

Based on the submitted data, reviews in Sections 7.R.2 and 7.R.3, and the applicant's explanation, it is appropriate to define the patient population for baricitinib as those with AD who, after a reasonable duration of treatment, had an inadequate response to appropriate treatment with topical anti-inflammatory drugs, such as TCS and TCI, or in whom topical anti-inflammatory drugs such as TCS are not recommended because of safety reasons.

Therefore, PMDA concluded that the indication of baricitinib should be specified as "atopic dermatitis in patients who have had an inadequate response to conventional treatments," and it is necessary to provide a cautionary statement to the effect that baricitinib should be used in patients with disease activity who, after a reasonable duration of treatment, had an inadequate response to appropriate treatment with topical anti-inflammatory drugs, such as TCS and TCI, including those in whom topical anti-inflammatory drugs such as TCS are not recommended. In addition, the applicant should provide healthcare professionals with information

on the inclusion/exclusion criteria used in the clinical studies to help them determine if a patient is eligible for treatment with baricitinib, and should provide a cautionary statement to the effect that baricitinib should be used by a physician with thorough knowledge in the diagnosis and treatment of AD so that an appropriate diagnosis is made, eligible patients are selected, and requirements for the proper use of the drug are met. While baricitinib can be easily administered orally, it may be associated with a risk for serious adverse reactions. Therefore, healthcare professionals should be advised to exercise particular caution to ensure that baricitinib is administered by experienced physicians at a medical institution with adequate facilities to respond to emergencies.

The PMDA's conclusion above will be discussed at the Expert Discussion.

7.R.4.2 Clinical positioning

The applicant's explanation about the clinical positioning of baricitinib:
Currently recommended pharmacotherapies for AD include topical anti-inflammatory drugs, such as TCS and TCI, in combination with the regular use of emollients, as well as the use of oral antihistamines as an adjuvant therapy. Patients who have had an inadequate response to these therapies may receive intermittent oral ciclosporin or subcutaneous dupilumab. The use of oral corticosteroids may be considered for induction of remission in AD patients with acute exacerbation or severe or the most severe conditions (Clinical Practice Guidelines for the Management of Atopic Dermatitis 2018 [in Japanese]. *Jpn J Dermatol.* 2018;128:2431-2502).

In line with the above treatment strategy, clinical studies were conducted in patients with moderate to severe AD who had an inadequate response to topical anti-inflammatory drugs and a certain level of disease activity, requiring systemic treatment [see Section 7.R.1]. Since the studies demonstrated the efficacy and safety of baricitinib in the patient population, baricitinib can be positioned as one of treatment options, along with other approved systemic drugs for AD, for patients with AD who had an inadequate response to appropriate treatment with topical anti-inflammatory drugs. In the clinical studies of baricitinib, concomitant use of ciclosporin, other oral JAK inhibitors, and biologics was prohibited, and therefore, no data are available regarding the use of baricitinib in combination with such drugs. Therefore, a cautionary statement to the effect that baricitinib in combination with these drugs or other potent immunosuppressants is not recommended will be included in the package insert and other materials.

PMDA's view:
Based on the submitted clinical study results and the latest treatment strategy for AD, baricitinib can be positioned as one of treatment options, along with other approved systemic drugs for AD, as explained by the applicant. It is also appropriate to advise against the use of baricitinib in combination with potent immunosuppressants such as ciclosporin, other oral JAK inhibitors, or biologics in patients with AD, for the following reasons: (i) baricitinib has immunosuppressive effects; (ii) no data are available regarding the use of baricitinib in combination with ciclosporin, other oral JAK inhibitors, or biologics; and (iii) caution has been

advised against using baricitinib in combination with other oral JAK inhibitors or biologic antirheumatic drugs that are positioned similarly to baricitinib for the treatment of RA.

The PMDA's conclusion above will be discussed at the Expert Discussion.

7.R.5 Dosage and administration

7.R.5.1 Dosage regimen

The applicant's explanation:

In the clinical studies, the efficacy of the 4 mg dose was consistently higher than that of the 2 mg dose, and a clinically significant improvement was observed in the 2 mg group compared to placebo for multiple endpoints. Thus, the dose may be reduced after assessment of the benefits and risks of individual patients. The proposed dosage regimen was specified as the same as that of the approved dosage regimen: "The usual adult dosage is 4 mg of baricitinib administered orally once daily. The dose should be reduced to 2 mg according to the patient's condition." Based on the data from the population pharmacokinetic analyses using the results from clinical studies in patients with AD [see Section 6.2.1], the dosage regimen of 2 mg once daily is appropriate for patients with moderate renal impairment, as with the dosage regimen for patients with RA.

PMDA's view:

Based on the submitted data and the reviews in Sections 7.R.2 and 7.R.3, the usual dosage regimen of baricitinib should be 4 mg once daily and the dosage regimen for patients with moderate renal impairment should be 2 mg once daily. As described in Section 7.R.2, baricitinib 2 mg is also expected to have a certain level of efficacy; therefore, the following statement can be added to the dosage regimen: "The dose should be reduced to 2 mg according to the patient's condition."

The PMDA's conclusion above will be discussed at the Expert Discussion.

7.R.5.2 Concomitant use of emollients and topical anti-inflammatory drugs such as TCS and TCI

The applicant's explanation about the use of baricitinib in combination with emollients and topical anti-inflammatory drugs such as TCS and TCI:

Emollients are vital to the recovery and maintenance of the skin barrier function, and the protocols for the clinical studies specified the daily use of emolients; therefore, the regular use of emollients is required during treatment with baricitinib. A statement to this effect should be included in the package insert.

The efficacy of baricitinib versus placebo was demonstrated in the studies evaluating baricitinib monotherapy (BREEZE-AD1 and BREEZE-AD2) and the studies evaluating baricitinib in combination with TCS (BREEZE-AD7 and BREEZE-AD4). Because baricitinib can be used with or without topical anti-inflammatory drugs, there would be no need for a cautionary statement to the effect that baricitinib must be administered in combination with topical anti-inflammatory drugs. In January 2020, a topical JAK inhibitor delgocitinib was approved as a topical anti-inflammatory drug with new mechanism of action for the treatment

of AD. Delgocitinib is potentially used in combination with baricitinib; therefore, the package insert will include a statement to the effect that there is no experience with the use of baricitinib in combination with topical JAK inhibitors.

PMDA's view:
The clinical studies demonstrated the efficacy of baricitinib with or without topical anti-inflammatory drugs, and serious safety concerns have not been raised. However, the concomitant use of emollients and topical anti-inflammatory drugs is regarded as the standard of care for AD in Japan. In addition, although comparison between studies has limitations, the efficacy of baricitinib in combination with TCS tended to be consistently higher than that of baricitinib alone. Therefore, baricitinib should be used in combination with topical anti-inflammatory drugs in principle, and with the regular use of emollients, and statements to this effect should be included in the package insert. While baricitinib is expected to be used in combination with topical JAK inhibitors, systemic exposure to delgocitinib, a currently approved topical JAK inhibitor, is extremely limited (Review Report of "Corectim Ointment 0.5%" dated October 10, 2019); therefore, for the time being, it is unnecessary to include a statement in the package insert to the effect that there is no experience with the use of baricitinib in combination with topical JAK inhibitors. However, in the use-results survey which was planned as part of post-marketing safety measures [see Section 7.R.6], data on concomitant treatments including topical JAK inhibitors should be collected and analyzed closely, based on which the need for further safety measures should be addressed.

The PMDA's conclusion above will be discussed at the Expert Discussion.

7.R.6 Post-marketing investigations and safety measures

The applicant plans to conduct a use-results survey (target sample size, 500 patients; follow-up period, 68 weeks) in addition to regular pharmacovigilance activities to assess the safety and efficacy of baricitinib in post-marketing clinical practice.

PMDA's view:
As discussed in Section 7.R.3, the safety data have raised no new safety concerns specific to patients with AD compared to the safety profile of baricitinib in the approved RA indication, except for skin infections. Because skin infections can be managed by providing appropriate cautionary advice regarding skin infections, the safety of baricitinib in patients with AD is acceptable. However, in the post-marketing setting, baricitinib is expected to be used in combination with drugs which have never been concomitantly used with baricitinib in the clinical studies; therefore, the applicant should conduct a use-results survey to evaluate the safety of baricitinib in clinical practice, as planned. In addition, based on the review presented in Section 7.R.2, the use-results survey should be designed to allow as much efficacy data as possible to be collected from patients on chronic treatment with baricitinib and patients receiving baricitinib at a reduced dose (including cases of increased dose levels following dose reduction). The applicant should provide safety and other data to healthcare professionals in an appropriate manner if new findings become available.

Further, it is important to make sure that baricitinib is used by a physician with thorough knowledge of baricitinib and sufficient knowledge and experience in the treatment of AD, and that patients with serious infections are treated by such physicians in cooperation with other departments and medical institutions, as necessary. To promote the proper use of baricitinib, the applicant should provide relevant information to physicians and other healthcare professionals using materials.

The PMDA's conclusion above and need for further safety measures will be discussed at the Expert Discussion.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1.2, CTD 5.3.5.1.3, CTD 5.3.5.1.4, and CTD 5.3.5.1.5.2) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that baricitinib has efficacy in the treatment of atopic dermatitis in patients who have had an inadequate response to conventional treatments and that baricitinib has acceptable safety in view of its benefits. Baricitinib is clinically meaningful because it offers a new treatment option for patients with AD who have had an inadequate response to conventional treatments. In post-marketing surveillance, the safety and other aspects of baricitinib in Japanese patients with AD in clinical practice should be further evaluated.

PMDA has concluded that baricitinib may be approved if it is not considered to have any particular problem based on the comments from the Expert Discussion.

10. Other

The method of efficacy evaluation and the definition of endpoints used in the clinical studies of baricitinib are summarized.

Measure	Description
EASI	The EASI is used to score the extent of disease, based on rating scales for percent BSA involvement (0 = 0%, 1 = 1% to 9%, 2 = 10% to 29%, 3 = 30% to 49%, 4 = 50% to 69%, 5 = 70% to 89%, 6 = 90% to 100%), and the severity of 4 clinical signs (erythema, edema/papulation, excoriation, and lichenification) each on a scale of 0 to 3 (0 = none, 1 = mild, 2 = moderate, 3 = severe) at 4 body regions (head and neck, trunk, upper extremities, and lower extremities). The score for each body region is derived by multiplying the sum of severity score for each region by the score for BSA involvement. Each region score is multiplied by the body region coefficient (head and neck = 0.1, trunk = 0.3, upper extremities = 0.2, lower extremities = 0.4). The resulting scores are added to obtain the total score. A total score of 0 (no symptoms); 0.1 to 1.0 (near remission); 1.1 to 7.0 (mild); 7.1 to 21.0 (moderate); 21.1 to 50.0 (severe); 50.1 to 72.0 (very severe)
IGA	The validated Investigator's global assessment of the patient's overall severity of AD on a 5-point scale according to the following criteria: 0 = clear (no inflammatory signs of AD. Post-inflammatory hyperpigmentation and/or hypopigmentation may be present) 1 = almost clear (barely perceptible erythema, barely perceptible induration/papulation, and/or minimal lichenification. No oozing or crusting. 2 = mild (slight but definite pinkish erythema, slight but definite induration/papulation, and/or slight but definite lichenification. No oozing or crusting.) 3 = moderate (clearly perceptible dark red erythema, clearly perceptible induration/papulation, and/or clearly perceptible lichenification. Oozing/crusting may be present.) 4 = severe (marked deep/bright red erythema, marked induration/papulation, and/or marked lichenification. Widespread lesions. Oozing/crusting may be present.)
Itch NRS	The itch NRS is 11-point horizontal scale anchored at 0 and 10, with 0 representing "no itch" and 10 representing "worst itch imaginable." Overall severity of itching is obtained by the patient's selection of the number that best describes the worst level of itching in the past 24 hours.
EASI50 EASI75 EASI90	The proportion of subjects achieving EASI50, EASI75, and EASI90 (% change from baseline is decreased by ≥50%, ≥75%, and ≥90%, respectively)
IGA 0 or 1	The proportion of subjects with an IGA score of 0 or 1, AND decreased from baseline by ≥2 points (Only in the BREEZE-AD3 study, the proportion of subjects with an IGA score of 0 or 1)
IGA 0, 1, or 2	The proportion of subjects with an IGA score of 0, 1, or 2

Definition for the footnotes for Table 26 and definition of events

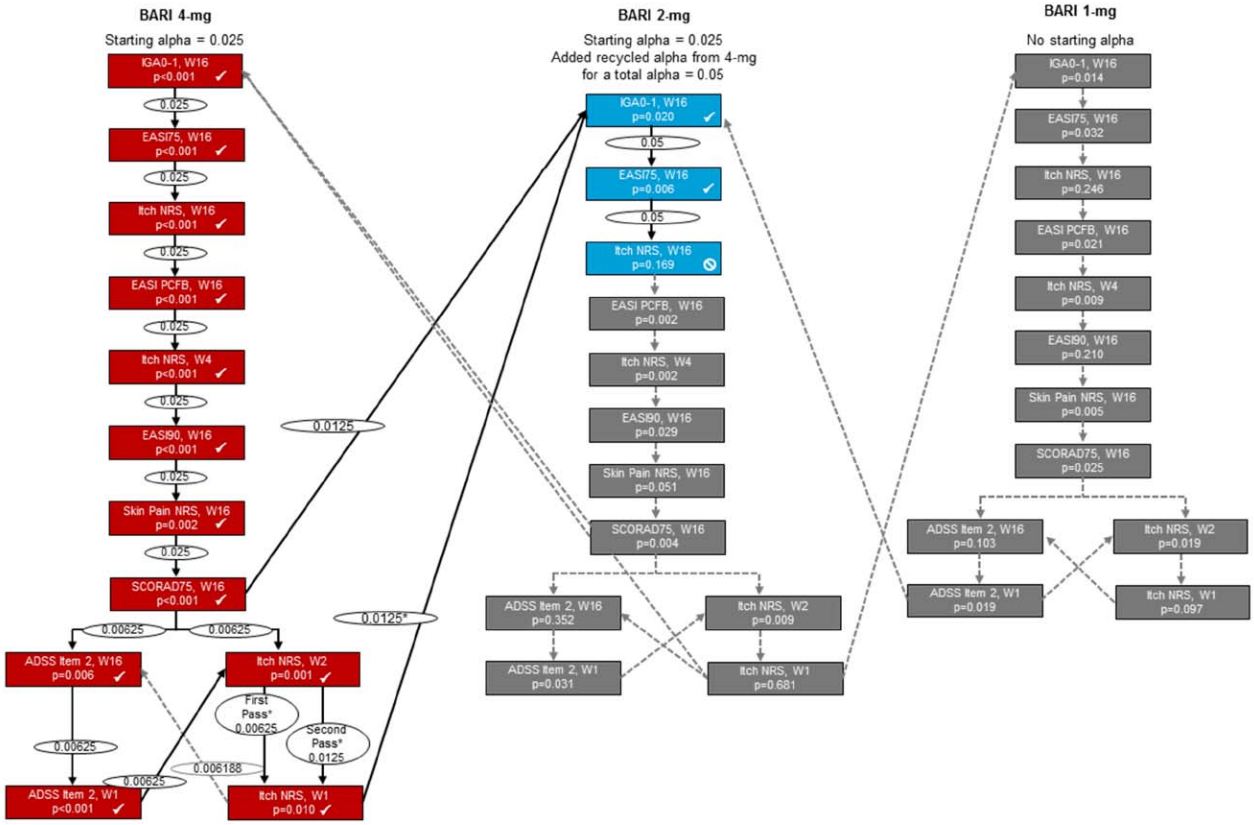
Definition for footnotes (Numbers in notes a) through h) represent the number of subjects evaluated) a) Anaemia, decreased neutrophils, decreased lymphocytes, ALP increased, ALT increased, AST increased, total bilirubin increased, serum creatinine increased (244), platelet count increased (243), CPK increased (241); b) CPK increased, ALP increased, ALT increased, AST increased, total bilirubin increased, serum creatinine increased (248), decreased neutrophils, decreased lymphocytes (247), anaemia, platelet count increased (246); c) anaemia, decreased neutrophils, ALP increased, ALT increased, AST increased, total bilirubin increased (487), decreased lymphocytes, serum creatinine increased (486), platelet count increased (485), CPK increased (483); d) anaemia, decreased neutrophils, decreased lymphocytes, ALP increased, ALT increased, AST increased, total bilirubin increased, serum creatinine increased (326), platelet count increased (325), CPK increased (323); e) anaemia, decreased neutrophils, decreased lymphocytes, ALP increased, ALT increased, AST increased, total bilirubin increased, serum creatinine increased (240), CPK increased (239), platelet count increased (236); f) ALP increased, ALT increased, AST increased, total bilirubin increased, serum creatinine increased (243), anaemia (241), decreased neutrophils, decreased lymphocytes, CPK increased (240), platelet count increased (239); g) ALP increased, ALT increased, AST increased, total bilirubin increased (2,136), anaemia, serum creatinine increased (2,134), decreased neutrophils (2,133), decreased lymphocytes (2,131), platelet count increased (2,121), CPK increased (2,111); h) anaemia, ALP increased, ALT increased, AST increased, total bilirubin increased (3,741), decreased lymphocytes (3,736), platelet count increased (3,716), decreased neutrophils (3,620), CPK increased (3,560), serum creatinine increased (3,545), MACE (3,251); i) calculated based on the exposure time including the follow-up period (10,301 PY); j) calculated using the data from the phase II and III studies (exposure time: 9,504.5 PY)
Definition of events All events were defined as events based on the MedDRA queries prepared by the applicant or medical reviews, except for the following: Infections, infections and infestations (SOC); serious infections, serious infection events; interstitial lung disease, interstitial lung disease (PT); anaemia, hemoglobin <4.9 mmol/L; decreased neutrophils, neutrophil count $<1.0 \times 10^9$/L; decreased lymphocytes, lymphocyte count $<0.5 \times 10^9$/L; platelet count increased, platelet count increased from ≤600,000/mm^3 to >600,000/mm^3; pancytopenia, pancytopenia (PT); CPK increased, >5 × ULN; ALP increased, ≥1.5 × ULN; ALT increased, ≥3 × ULN; AST increased, ≥3 × ULN; total bilirubin increased, ≥2 × ULN; serum creatinine increased, >3 × ULN; depression or suicidal/self-injurious behavior, depression and suicide/self-injury (SMQ)

Table 27 and definition of events

Definition for the footnotes (Numbers in notes a) through c) represent the number of subjects evaluated) a) decreased neutrophils, decreased lymphocytes, platelet count increased, CPK increased (43); b) anaemia, decreased neutrophils, decreased lymphocytes, CPK increased, ALP increased, ALT increased, AST increased, total bilirubin increased, serum creatinine increased (340), platelet count increased (339); c) platelet count increased (513), MACE, serum creatinine increased (371); d) calculated based on the exposure time including the follow-up period (1,269.5 PY); e) calculated using the data from the phase II and III studies (1,097.3 PY)
Definition of events See definitions in Table 26

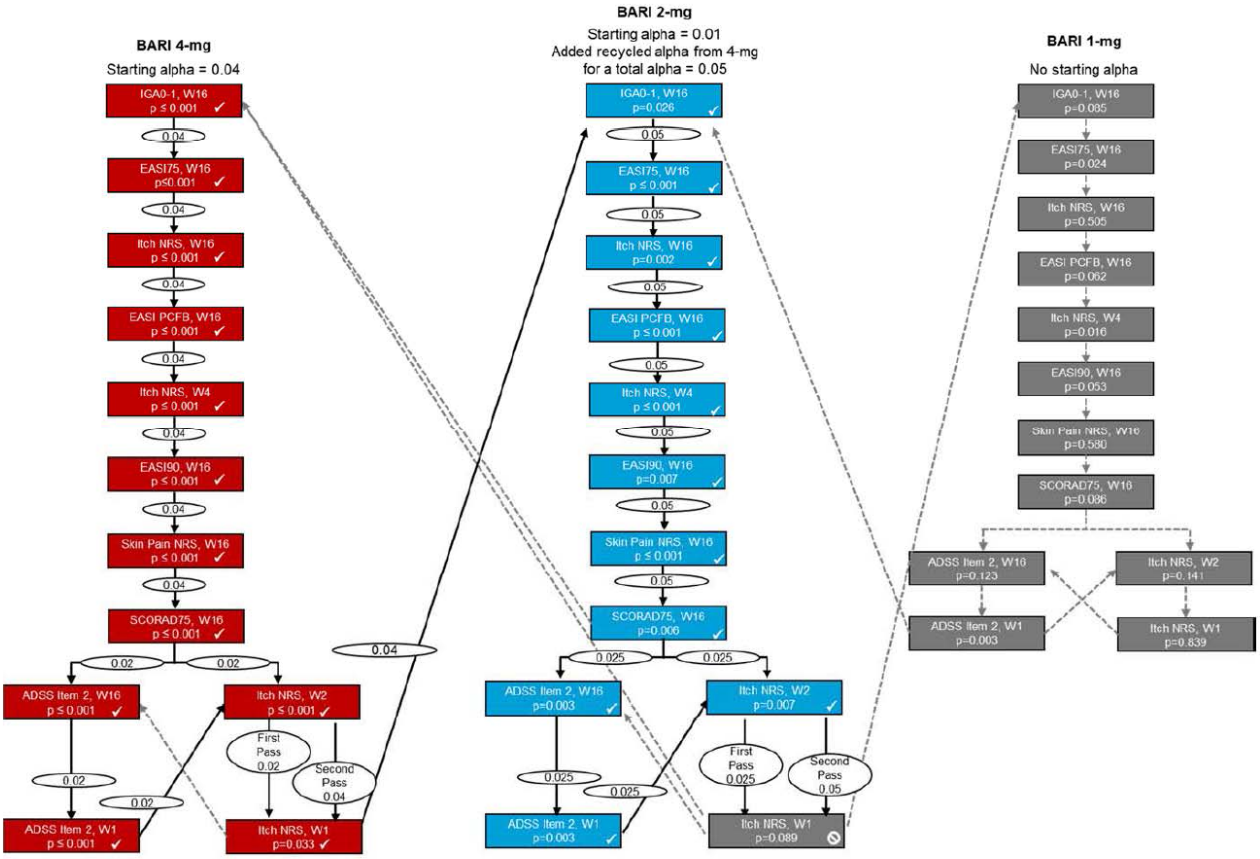
A graphical approach was used for adjustment of multiplicity in the analyses of the primary endpoint and secondary endpoints in the clinical studies. The details of the graphical approach are shown below.

BREEZE-AD1 study



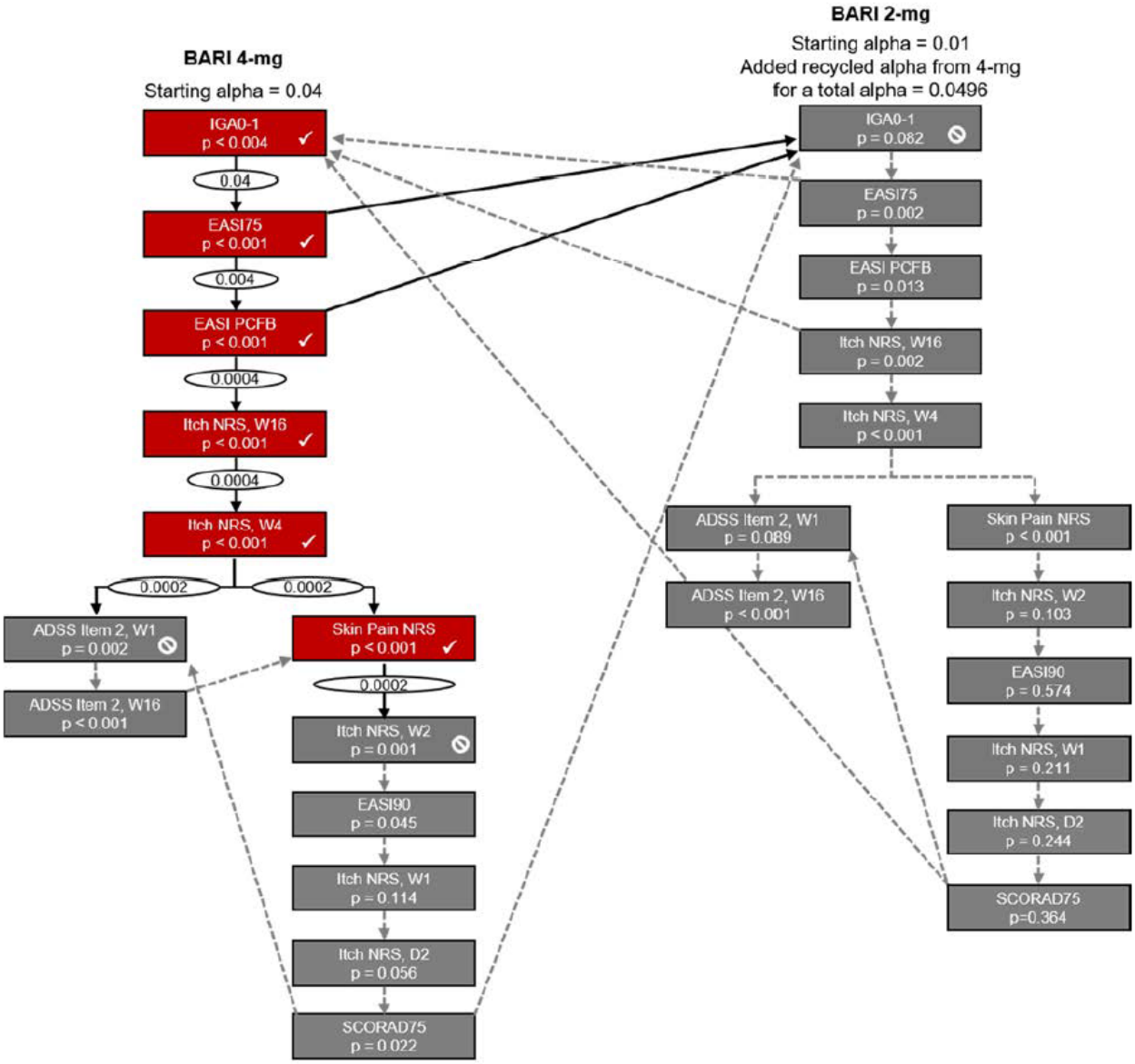
The number in an oval with a black arrow shows the significance level allocated. A check mark indicates that the endpoint is statistically significant in the graphical approach. A stop symbol indicates that the endpoint is not statistically significant, and the hypothesis testing by the graphical approach has been stopped. A dotted arrow indicates that the significance level was not allocated.

BREEZE-AD2 study



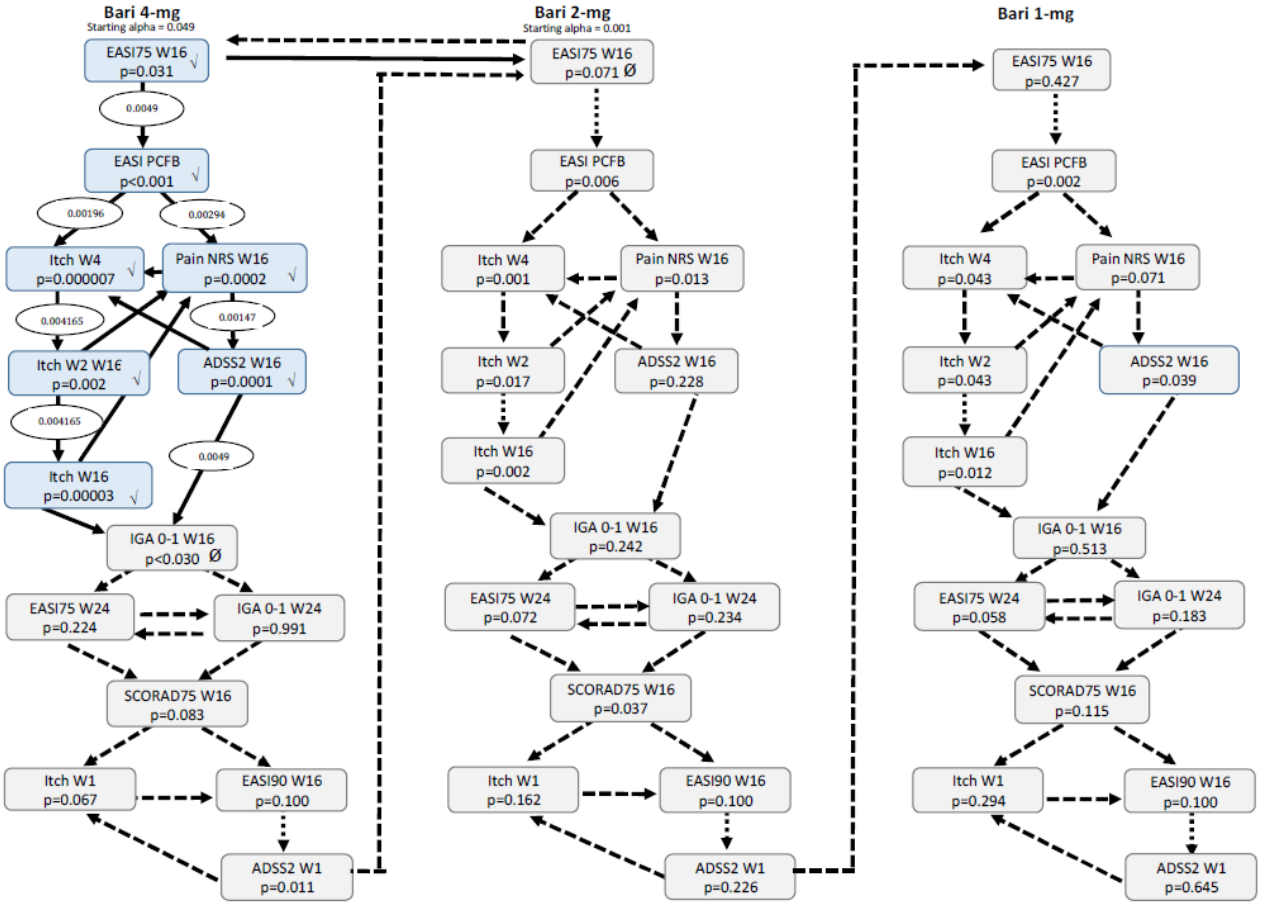
The number in an oval with a black arrow shows the significance level allocated. A check mark indicates that the endpoint is statistically significant in the graphical approach. A stop symbol indicates that the endpoint is not statistically significant, and the hypothesis testing by the graphical approach has been stopped. A dotted arrow indicates that the significance level was not allocated.

BREEZE-AD7 study



The number in an oval with a black arrow shows the significance level allocated. A check mark indicates that the endpoint is statistically significant in the graphical approach. A stop symbol indicates that the endpoint is not statistically significant, and the hypothesis testing by the graphical approach has been stopped. A dotted arrow indicates that the significance level was not allocated.

BREEZE-AD4 study



The number in an oval with a black arrow shows the significance level allocated. A check mark indicates that the endpoint is statistically significant in the graphical approach. A stop symbol indicates that the endpoint is not statistically significant, and the hypothesis testing by the graphical approach has been stopped. A dotted arrow indicates that the significance level was not allocated.

Review Report (2)

November 25, 2020

Product Submitted for Approval

Brand Name	Olumiant Tablets 2 mg Olumiant Tablets 4 mg
Non-proprietary Name	Baricitinib
Applicant	Eli Lilly Japan K.K.
Date of Application	January 29, 2020

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy, indications, dosage and administration, and clinical positioning

At the Expert Discussion, the expert advisors largely supported the PMDA's conclusions on the efficacy, indications, dosage and administration, and clinical positioning of baricitinib presented in Review Report (1). The following comments were made by the expert advisors:

- In the BREEZE-AD7 study, the results for the 4 mg group in the Japanese subpopulation tended to be inconsistent with those in the overall study population. Though this requires caution, the efficacy of baricitinib 4 mg has been demonstrated by the submitted clinical study results, and the 2 mg dose is also expected to be effective.
- The package insert should include information regarding the time to achieve response with baricitinib as a guide based on the data from clinical studies.

Based on the reviews in Section "7.R.6 Post-marketing investigations and safety measures" in the Review Report (1) and at the Expert Discussion and, PMDA considers that the applicant should collect as much efficacy data as possible in post-marketing surveillance, including data from patients on chronic treatment with baricitinib and patients receiving baricitinib at a reduced dose (including cases of increased dose levels following dose reduction), and should appropriately communicate new information to healthcare professionals in clinical practice if it becomes available. The unnecessary chronic use of baricitinib should be prevented. To this end, PMDA concluded that the package insert should include information regarding the time to onset of

response to baricitinib as a guide (8 weeks of treatment) based on the data from clinical studies,[18] and that the package insert should also include a statement to the effect that treatment discontinuation should be considered if response has not achieved within the timeframe specified. PMDA requested the applicant to provide appropriate advice in this regard and the applicant agreed with the instruction.

1.2 Safety, post-marketing safety measures, and risk management plan (draft)

At the Expert Discussion, the expert advisors largely supported the PMDA's conclusions on the safety of baricitinib and post-marketing safety measures presented in Review Report (1). The following comments were made by the expert advisors:

- Even if topical JAK inhibitors is concomitantly used, systemic exposure to those topical drugs is extremely limited. It is unlikely that systemic adverse reactions associated with the use of baricitinib are intensified by such drugs. However, baricitinib may increase the risk for skin infection; therefore, caution should be exercised especially for the risk of topical adverse events during treatment with baricitinib in combination with topical JAK inhibitors.

PMDA requested the applicant to appropriately provide healthcare professionals with information on concomitant drugs/therapies in the clinical studies of baricitinib by utilizing information materials. PMDA also requested the applicant to closely examine the collected data regarding concomitant drugs/therapies in post-marketing surveillance, and to consider suitable ways of information provision and need for additional safety measures. The applicant agreed with the instruction.

In view of the discussion above, PMDA has concluded that the risk management plan (draft) for baricitinib should include the safety specification presented in Table 30, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 31. PMDA requested the applicant to conduct post-marketing surveillance to facilitate investigation of the above issues.

Table 30. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Herpes zoster • Serious infections (including tuberculosis, pneumonia, pneumocystis pneumonia, sepsis, opportunistic infection) • Gastrointestinal perforation • Reactivation of hepatitis B virus • Interstitial lung disease • Neutrophil count decreased, lymphocyte count decreased, haemoglobin decreased • Hepatic dysfunction • Venous thromboembolism	• Rhabdomyolysis, myopathy • Malignancy • Cardiovascular events	None
Efficacy specification		
• Efficacy of baricitinib in clinical practice (rheumatoid arthritis)		

(No change)

[18] In the BREEZE-AD7 study, the negative predictive value for achievement of Week 16 IGA (0/1) by IGA (0/1/2) at Week 8 was 0.94, the negative predictive value for achievement of Week 16 EASI75 by EASI50 at Week 8 was 0.93, the negative predictive value for achievement of Week 16 itch NRS improvement ≥4 by itch NRS improvement ≥3 at Week 8 was 0.96.

Table 31. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy survey and studies	Additional risk minimization activities
• Early post-marketing phase vigilance (atopic dermatitis) • Specified use-results survey (rheumatoid arthritis) • Specified use-results survey (atopic dermatitis) • Post-marketing database survey (serious infections) (rheumatoid arthritis) • Post-marketing database survey (malignancies) (rheumatoid arthritis) • Post-marketing clinical study (the JADY study) (rheumatoid arthritis) • Post-marketing clinical study (the JAHN study) (atopic dermatitis)[a)] • Post-marketing clinical study (the JAIN study) (atopic dermatitis)[a)]	• Specified use-results survey (rheumatoid arthritis)	• Prepare and disseminate written information for healthcare professionals (a proper use guide) • Prepare and disseminate written information for patients (“For patients taking Olumiant”) • Ensure that information on proper use is provided before delivery • Disseminate data gathered during early post-marketing phase vigilance (atopic dermatitis)

a) After approval of the application for baricitinib for the treatment of AD, the BREEZE-AD3 (JAHN) and BREEZE-AD4 (JAIN) studies will be switched to post-marketing clinical studies

(Underline denotes additions for the present application)

The applicant’s explanation:

As shown in Table 32, a specified use-results survey will be conducted in patients with AD who have had an inadequate response to conventional treatments, with a planned sample size of 500 patients for 68 weeks of follow-up to investigate the safety and efficacy of baricitinib in clinical practice.

Table 32. Outline of specified use-results survey (draft)

Objective	To collect and evaluate information on the safety and efficacy of baricitinib in clinical practice
Survey method	Central registry system
Population	Patients with AD who have had an inadequate response to conventional treatments
Observation period	68 weeks
Planned sample size	500 patients (for safety analysis)
Main survey items	• Safety specification: serious infections (including tuberculosis, pneumonia, pneumocystis pneumonia, sepsis, opportunistic infection) • Patient characteristics • Medical history/comorbidities • Treatment history of AD • Treatment status with baricitinib • Concomitant drugs/therapies • Adverse events • Clinical laboratory test results • Efficacy outcome measures (e.g., EASI, BSA, PRO, global assessment of improvement by physicians)

PMDA accepted the applicant’s actions. Gathered information should be communicated to healthcare professionals immediately and in a timely manner.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the proposed indications as shown below, with the following conditions for approval. Although the present application has been submitted for the addition of a drug with a new indication, the remainder of the re-examination period for the initial approval of the product is more than 4 years; therefore, the re-examination period for the present application is the remainder of the re-examination period for the initial approval of the product (until July 2, 2025).

Indications

The following diseases in patients who have had an inadequate response to conventional treatments:

Rheumatoid arthritis ~~in patients who have had an inadequate response to conventional treatments~~ (including the prevention of structural joint damage)
~~Moderate to severe~~ atopic dermatitis

(Underline denotes additions to the proposed text. Strikethrough denotes deletion from the proposed text.)

Dosage and Administration

The usual adult dosage is 4 mg of baricitinib administered orally once daily. The dose should be reduced to 2 mg according to the patient's condition.

(No change)

Approval Conditions

The applicant is required to develop and appropriately implement a risk management plan.

List of Abbreviations

AD	Atopic dermatitis
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
$AUC_{\tau,ss}$	AUC during one dosing interval at steady state
BMI	Body mass index
BSA	Body surface area
CI	Confidence interval
CL_{nr}/F	Apparent non-renal clearance
CL_r/F	Apparent renal clearance
$C_{max,ss}$	C_{max} during a dosing interval at steady state
CPK	Creatine phosphokinase
CV	Coefficient of variation
EASI	Eczema area and severity index
eGFR	Estimated glomerular filtration rate
HLT	High-level term
IGA	Investigator's global assessment
IL	Interleukin
ITT	Intent to treat
JAK	Janus kinase
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
MACE	Major adverse cardiovascular event
MedDRA	Medical dictionary for regulatory activities
MMRM	Mixed-effect model of repeated measure
NMSC	Non-melanoma skin cancers
NRI	Non-responder imputation
NRS	Numerical rating scale
OC	Observed cases
OCS	Oral corticosteroid
Olumiant	Olumiant Tablets 2 mg and Olumiant Tablets 4 mg
PMDA	Pharmaceuticals and Medical Devices Agency
PRO	Patient-reported outcome
PT	Preferred term
RA	Rheumatoid arthritis
SMQ	Standardized MedDRA queries
SOC	System organ class
STAT	Signal transducer and activator of transcription
TCS	Topical corticosteroids
TCI	Topical calcineurin inhibitor
ULN	Upper limit of normal
V_1/F	Apparent central volume of distribution