



# Pooled Safety Analysis of Baricitinib in Adult Participants with Atopic Dermatitis in the Japanese Subpopulation from Six Randomized Clinical Trials

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## ABSTRACT

**Introduction:** Baricitinib is an oral selective Janus kinase (JAK)1/JAK2 inhibitor approved in Japan and the European Union for the treatment of atopic dermatitis (AD). The aim of this study is to report pooled safety data for baricitinib in the Japanese subpopulation of the clinical development program in moderate-to-severe AD.

**Methods:** This analysis included participant-level safety data from five double-blind, randomized clinical studies and one double-blind, randomized, long-term extension study, reported in three datasets for the Japanese subpopulation: (1) placebo-controlled, (2) baricitinib 2 mg and 4 mg extended (“2-mg—4-mg extended”), and (3) all baricitinib doses (“All-bari-AD”). The data cutoff was 13 December 2019. Safety outcomes included treatment-emergent adverse events, adverse events of special

interest, and abnormal laboratory changes. Proportions of participants with events and incidence rates were calculated.

**Results:** Data were collected for 341 participants from Japan who received baricitinib for 371.7 participant-years (median duration 371.0 days). In the placebo-controlled dataset, the frequencies of serious infections and herpes zoster were low and similar between treatment groups, and the incidence of treatment-emergent infections, in particular herpes simplex, was higher in the baricitinib groups compared with the placebo group. No gastrointestinal perforations, tuberculosis, positively adjudicated cardiovascular events, deep vein thrombosis, or pulmonary embolism were reported with exposure up to 2 years in the All-bari-AD dataset. There were no deaths in the Japanese subpopulation.

**Conclusions:** This integrated safety analysis in the subpopulation of Japanese participants is consistent with the established safety profile of baricitinib in the global study population with moderate-to-severe AD.

**Clinicaltrials.gov identifiers:** NCT02576938, NCT03334396, NCT03334422, NCT03428100, NCT03733301, and NCT03334435.

**Keywords:** Asians; Atopic dermatitis; Baricitinib; Safety; Randomized controlled trial

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## Key Summary Points

### *Why carry out this study?*

A pooled analysis of safety data for baricitinib in participants with moderate-to-severe atopic dermatitis from eight clinical studies confirmed the established safety profile of baricitinib.

In this pooled analysis, the safety data for baricitinib in the Japanese subpopulation, which represented one of the major subpopulations in the pooled analysis, are reported from five placebo-controlled clinical studies and one long-term extension study with exposure up to 2 years.

### *What was learned from the study?*

In the placebo-controlled dataset, the frequencies of serious infections and herpes zoster were low and similar between treatment groups, and the incidence of treatment-emergent infections, in particular herpes simplex, was higher in the baricitinib groups compared with the placebo group.

In the dataset that included all baricitinib doses, no gastrointestinal perforations, tuberculosis, positively adjudicated cardiovascular events, deep vein thrombosis, or pulmonary embolism were reported with baricitinib exposure up to 2 years, and there were no deaths.

These findings in the subpopulation of Japanese participants are consistent with the established safety profile of baricitinib in the global study population with moderate-to-severe atopic dermatitis.

scaly, pruritic, erythematous lesions that can be located on almost any part of the body. The prevalence of AD in adults in Japan has been estimated to range from 2% to 9% [1–4]. While this estimated prevalence in Japan is similar to that of Western countries [4], there are likely to be some differences in disease phenotype for people from Japan. For instance, there is higher activation of Th17 in people from Asia compared with people from European and American countries [5]. Furthermore, mutations in the gene encoding filaggrin, which is a predisposing factor for AD, is less frequent in people from Japan compared with people from Europe [6].

Baricitinib is an oral selective Janus kinase (JAK)1/JAK2 inhibitor approved in Japan and the European Union for the treatment of AD [7]. Baricitinib has also been approved in Japan for the treatment of rheumatoid arthritis (RA) since July 2017, COVID-19 since April 2021, and alopecia areata since June 2022.

In completed phase 2 and 3 studies, baricitinib either as monotherapy or in combination with topical corticosteroids has been shown to significantly improve the signs and symptoms of moderate-to-severe AD compared with placebo [7–9]. A pooled analysis of safety data for baricitinib in 2531 participants with moderate-to-severe AD from six double-blind, randomized controlled studies, one double-blind, randomized, long-term extension study, and one open-label, long-term extension study, confirmed the established safety profile of baricitinib [10]. The frequency of serious infections, opportunistic infections, and conjunctival disorders was low and similar between treatment groups in the placebo-controlled dataset [10]. No malignancies, gastrointestinal perforations, positively adjudicated cardiovascular events, or active tuberculosis were reported in the placebo-controlled dataset in participants treated with baricitinib [10]. In participants who received any dose of baricitinib (the “All-bari-AD” dataset), there were two positively adjudicated major adverse cardiovascular events, two venous thrombosis events, and one death [10].

Participants from Japan represented one of the major subpopulations in the pooled analysis of safety data for baricitinib [10]. However, the effect of baricitinib on the Japanese

## INTRODUCTION

Atopic dermatitis (AD) is a chronic, relapsing, inflammatory skin condition characterized by

subpopulation with AD has not been explored in depth. In this pooled analysis, we report the safety data for baricitinib in moderate-to-severe AD from five placebo-controlled clinical studies and one long-term extension study with exposure up to 2 years in the Japanese subpopulation.

## METHODS

### Study Design and Participants

The study designs, eligibility criteria, datasets, safety outcomes, and statistical analyses for each study have been published previously [10]. Safety data were included from five double-blind, randomized clinical studies (phase 2: NCT02576938; phase 3: NCT03334396 [BREEZE-AD1], NCT03334422 [BREEZE-AD2], NCT03428100 [BREEZE-AD4], and NCT03733301 [BREEZE-AD7]) and one double-blind, randomized, long-term extension study (NCT03334435 [BREEZE-AD3]). All studies included participants from Japan. Overall, 341 participants (13.5%) were from Japan [10].

The study protocols were approved by local ethics committees and were conducted in accordance with the principles of the Declaration of Helsinki, Council of International Organizations of Medical Sciences International Ethical Guidelines, and Good Clinical Practice guidelines. All participants gave written informed consent before participation in the study.

### Analysis Datasets

Three integrated datasets were analyzed:

1. The “placebo-controlled” dataset assessed the safety profile of baricitinib 2 mg and 4 mg versus placebo during the 16-week, placebo-controlled period for participants in the phase 2 study and four phase 3 studies (BREEZE-AD1, BREEZE-AD2, BREEZE-AD4, and BREEZE-AD7).
2. The baricitinib 2 mg and 4 mg extended (“2-mg—4-mg extended”) dataset assessed the long-term safety profile from the randomized, long-term extension study BREEZE-AD3, and the 16-week placebo-controlled

data, including the phase 2 study and BREEZE-AD4. BREEZE-AD3 enrolled participants from originating studies BREEZE-AD1, BREEZE-AD2, and BREEZE-AD7, giving a total exposure up to 105 weeks of treatment. Data after dose change were treated as censored at dose change.

3. The all baricitinib doses (“All-bari-AD”) dataset provided estimates for incidence rates (IRs) of all adverse events (AEs), as well as assessment for less common event types, and included safety data during treatment with baricitinib, as well as the follow-up period after baricitinib treatment.

### Safety Outcomes

Treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), deaths, events leading to interruption or discontinuation of study drug, AEs of special interest (AESI), and abnormal laboratory changes were evaluated. For some AESI, cluster analyses grouped preferred terms (PTs) and terms associated with related clinical disease presentations. These clusters were informed by combining Medical Dictionary for Regulatory Activities (MedDRA) standardized MedDRA queries, medical assessment of PTs, and clusters previously used to establish the safety profile of baricitinib in RA.

### Statistical Analysis

As the ratio for randomization of baricitinib to placebo varied across all the studies, adjusted percentages and adjusted IRs were calculated for AEs to provide appropriate direct comparisons between treatment groups for the placebo-controlled and 2-mg—4-mg extended datasets. Adjusted percentages were derived using study weights based on total sample size per study. Adjusted IRs per 100 participant-years at risk of observation time, with observation time censored at event date, were derived using study weights based on total participant-years of exposure per study. For the All-bari-AD dataset, IRs were calculated as the number of participants with an event per 100 participant-years at risk of

observation time, with observation time censored at event date. The observation time included a 30-day follow-up period following discontinuation of baricitinib treatment.

## RESULTS

### Study Participants in the Japanese Subpopulation

At baseline, participant demographics and measures of disease activity were similar

between baricitinib doses (2 mg and 4 mg) and placebo and across all datasets (Table 1).

### Treatment-Emergent Adverse Events in the Japanese Subpopulation

In the placebo-controlled dataset, 44.9%, 54.4%, and 57.3% of participants in the placebo, baricitinib 2 mg, and baricitinib 4 mg groups, respectively, reported  $\geq 1$  TEAE (Table 2). Most TEAEs were mild or moderate in severity (data not shown).

**Table 1** Baseline demographics and measures of disease activity in the Japanese subpopulation

	Placebo controlled (to week 16)			All-bari-AD <sup>a</sup> , N = 341
	Placebo, N = 134	Baricitinib 2 mg, N = 101	Baricitinib 4 mg, N = 89	
Age, years	35.9 (10.9)	35.6 (11.1)	34.2 (11.3)	35.7 (11.0)
Female, n (%)	36 (26.9)	22 (21.8)	19 (21.3)	87 (25.5)
Body mass index, kg/m <sup>2</sup>	24.0 (4.5)	23.8 (4.1)	23.6 (3.9)	23.8 (4.1)
Duration since AD diagnosis, years	25.3 (13.5)	23.2 (12.7)	23.1 (12.9)	24.9 (12.7)
Geographic region Japan, n (%)	134 (100)	101 (100)	89 (100)	341 (100)
Prior topical therapy				
Corticosteroids, n (%)	132 (98.5)	101 (100)	89 (100)	337 (98.8)
Calcineurin inhibitor, n (%)	80 (64.5)	60 (70.6)	58 (73.4)	211 (68.7)
Prior systemic therapy				
Cyclosporine, n (%)	17 (14.9)	17 (25.0)	11 (15.7)	49 (17.8)
Disease characteristics				
vIGA-AD score of 4 (severe disease), n (%)	55 (43.7)	40 (42.1)	35 (42.2)	143 (43.5)
EASI score	35.2 (14.2)	33.9 (13.4)	34.7 (12.5)	34.9 (13.5)
SCORAD	69.8 (14.5)	67.9 (14.4)	69.1 (13.1)	69.2 (14.2)
Percent body surface area affected	63.2 (21.6)	60.5 (20.9)	62.1 (21.5)	62.2 (21.4)
DLQI	11.2 (6.3)	11.8 (6.7)	10.6 (6.2)	11.4 (6.6)
Itch NRS	6.7 (2.0)	6.7 (2.1)	6.3 (2.2)	6.5 (2.1)

Data presented as mean (standard deviation) unless otherwise indicated

AD atopic dermatitis, *All-bari-AD* participants who received any dose of baricitinib, *DLQI* Dermatology Life Quality Index, *EASI* Eczema Area and Severity Index, *NRS* numeric rating scale, *SCORAD* SCORing Atopic Dermatitis; *vIGA-AD*, validated Investigator Global Assessment for Atopic Dermatitis

<sup>a</sup>All baricitinib doses includes the baricitinib 1 mg, 2 mg, and 4 mg doses

**Table 2** Overview of safety measures including drug exposure, treatment-emergent adverse events, and adverse events of special interest in the Japanese subpopulation

	Placebo controlled (to week 16)			2-mg–4-mg extended		All-bari-AD <sup>a</sup> , N = 341
	Placebo, N = 134	Baricitinib 2 mg, N = 101	Baricitinib 4 mg, N = 89	Baricitinib 2 mg, N = 101	Baricitinib 4 mg, N = 89	
Exposure						
Total participant-years	39.1	30.7	26.9	78.6	93.2	371.7
Participants with ≥ 52 weeks, n (%)	–	–	–	32 (31.7)	43 (48.3)	201 (58.9)
Median duration, days	113.0	113.0	113.0	315.0	362.0	371.0
Longest exposure, days	121	120	119	675	702	703
Adverse events, n (adj %) [adj IR] <sup>b</sup>						
Any TEAE	63 (44.9) [229.1]	51 (54.4) [261.0]	52 (57.3) [310.3]	60 [197.7]	69 [200.7]	245 [149.3]
SAE	3 (1.9) [6.7]	0	3 (2.9) [9.3]	2 [1.6]	6 [6.0]	13 [3.5]
Interruption of study drug due to AE	0	1 (1.4) [4.7]	2 (2.5) [8.6]	3 [3.3]	5 [6.4]	17 [4.6]
Discontinuation of study drug due to AE	0	2 (2.2) [6.9]	5 (4.5) [13.8]	2 [2.6]	7 [7.0]	16 [4.2]
Death, n (IR)	0	0	0	0	0	0
Infections, n (adj %) [adj IR] <sup>b</sup>						
Treatment-emergent infections	34 (25.2) [100.0]	35 (36.3) [146.9]	35 (40.0) [165.0]	45 [108.6]	51 [105.7]	187 [84.9]
Serious infection	0	0	1 (1.3) [4.0]	2 [1.6]	2 [1.8]	5 [1.3]
Herpes zoster	0	1 (1.4) [4.7]	0	1 [1.4]	2 [2.6]	9 [2.4]
Herpes simplex <sup>c</sup>	3 (1.9) [6.5]	5 (5.4) [18.3]	7 (8.0) [27.0]	9 [10.9]	9 [10.1]	29 [8.1]
Eczema herpeticum <sup>d</sup>	0	1 (1.4) [4.7]	4 (5.2) [17.9]	2 [2.5]	4 [4.7]	8 [2.1]
Skin infections needing antibiotic treatment	8 (7.1) [24.6]	6 (5.1) [17.3]	3 (3.5) [11.2]	6 [7.1]	3 [3.0]	13 [3.6]
TB	0	0	0	0	0	0

Table 2 continued

	Placebo controlled (to week 16)			2-mg—4-mg extended		All-bari-AD <sup>a</sup> , N = 341
	Placebo, N = 134	Baricitinib 2 mg, N = 101	Baricitinib 4 mg, N = 89	Baricitinib 2 mg, N = 101	Baricitinib 4 mg, N = 89	
Opportunistic infection excl TB	0	0	0	0	1 [1.7]	1 [0.3]
Malignancy, <i>n</i> (adj %) [adj IR] <sup>b</sup>						
Malignancy excluding NMSC	0	0	0	0	0	2 [0.52]
NMSC	0	0	0	0	0	0
Adverse CV events, <i>n</i> (adj %) [adj IR] <sup>b</sup>						
MACE	0	0	0	0	0	0
VTE (DVT and/or PE)	0	0	0	0	0	0
PE	0	0	0	0	0	0
GI disorders, <i>n</i> (adj %) [adj IR] <sup>b</sup>						
GI perforations	0	0	0	0	0	0
Ocular adverse events, <i>n</i> (adj %) [adj IR] <sup>b</sup>						
Conjunctival disorders	4 (2.8) [9.7]	0	1 (1.3) [4.2]	0	1 [0.9]	7 [1.9]

*adj* adjusted, *AE* adverse events, *All-bari-AD* participants who received any dose of baricitinib, *CV* cardiovascular, *DVT* deep vein thrombosis, *excl* excluding, *GI* gastrointestinal, *IR* incidence rate, *MACE* major adverse cardiovascular events, *NMSC* nonmelanoma skin cancer, *PE* pulmonary embolism, *SAE* serious adverse event, *TB* tuberculosis, *VTE* venous thromboembolism

<sup>a</sup>All baricitinib doses includes the baricitinib 1 mg, 2 mg, and 4 mg doses

<sup>b</sup>IRs for the placebo-controlled datasets and the baricitinib 2 mg and 4 mg datasets are study-size adjusted rates; adjusted percentages are only shown for the placebo-controlled dataset

<sup>c</sup>Herpes simplex included preferred terms of herpes simplex, oral herpes, Kaposi's varicelliform eruption, eczema herpeticum, ophthalmic herpes simplex, genital herpes, and genital herpes simplex

<sup>d</sup>Contains the preferred terms eczema herpeticum and Kaposi's varicelliform eruption

In the placebo-controlled dataset, 1.9%, 0%, and 2.9% of participants in the placebo, baricitinib 2 mg, and baricitinib 4 mg groups, respectively, reported SAEs (Table 2). There were no deaths among participants from Japan.

Treatment-emergent infections were the most common AESI in all three datasets

(Table 2). In the placebo-controlled dataset, the incidence of treatment-emergent infections, in particular herpes simplex, was higher in the baricitinib groups compared with the placebo group. However, there did not appear to be a noteworthy difference between baricitinib doses. The IRs for treatment-emergent infec-

**Table 3** Adverse event details for participants in the Japanese subpopulation

	Placebo controlled (to week 16)			2-mg–4-mg extended		All-bari-AD <sup>a</sup> , N = 341
	Placebo, N = 134	Baricitinib 2 mg, N = 101	Baricitinib 4 mg, N = 89	Baricitinib 2 mg, N = 101	Baricitinib 4 mg, N = 89	
TEAE occurring in $\geq 2\%$ of participants in any group in the placebo-controlled datasets, n (adj %) [adj IR]						
Nasopharyngitis	18 (13.3) [48.1]	16 (16.9) [60.8]	21 (24.0) [90.5]	23 [44.3]	32 [51.7]	97 [32.8]
Kaposi's varicelliform eruption	0	1 (1.4) [4.7]	4 (5.2) [17.9]	2 [2.5]	4 [4.7]	8 [2.1]
Acne	3 (1.9) [6.6]	1 (1.4) [4.7]	4 (4.6) [15.4]	5 [6.9]	8 [9.8]	26 [7.2]
Herpes simplex	2 (1.3) [4.3]	2 (2.7) [8.9]	3 (3.3) [10.9]	4 [5.5]	6 [5.9]	17 [4.6]
Headache	2 (1.3) [4.3]	5 (6.3) [21.2]	3 (2.9) [9.2]	6 [9.6]	3 [3.1]	14 [3.8]
Folliculitis	3 (2.7) [9.1]	5 (4.8) [16.8]	3 (2.8) [9.4]	9 [11.5]	4 [4.1]	29 [8.1]
Abdominal pain upper	1 (0.6) [2.2]	0	2 (2.6) [8.3]	0	2 [1.9]	2 [0.5]
Tonsillitis	2 (1.3) [4.4]	1 (0.6) [2.2]	2 (2.5) [8.5]	2 [1.7]	2 [2.7]	4 [1.1]
Blood creatine increased	0	0	2 (2.5) [8.0]	0	2 [1.8]	2 [0.5]
Hyperuricemia	0	0	2 (2.1) [6.6]	0	2 [2.0]	2 [0.5]
Upper respiratory tract infection	2 (1.4) [4.8]	0	2 (2.0) [6.4]	0	3 [2.9]	8 [2.1]
Skin papilloma	0	2 (2.0) [6.9]	1 (1.3) [4.6]	4 [5.7]	4 [4.6]	13 [3.5]
Eczema	0	2 (2.7) [8.9]	1 (1.3) [4.0]	3 [5.2]	2 [1.8]	5 [1.3]
Otitis externa	0	4 (3.5) [11.4]	1 (1.3) [4.1]	5 [6.2]	1 [0.9]	12 [3.2]

Table 3 continued

	Placebo controlled (to week 16)			2-mg—4-mg extended		All-bari-AD <sup>a</sup> , N = 341
	Placebo, N = 134	Baricitinib 2 mg, N = 101	Baricitinib 4 mg, N = 89	Baricitinib 2 mg, N = 101	Baricitinib 4 mg, N = 89	
Dyshidrotic eczema	0	3 (3.5) [11.6]	1 (0.7) [2.4]	4 [6.4]	3 [2.9]	10 [2.7]
Permanent discontinuation of study drug due to adverse event by system organ class, n (adj %) [adj IR]						
Skin and subcutaneous tissue disorders <sup>b</sup>	0	1 (0.9) [2.3]	3 (2.4) [7.3]	1 [0.9]	3 [3.1]	5 [1.3]
Infections and infestations	0	1 (1.4) [4.6]	1 (1.3) [4.0]	1 [1.7]	1 [0.9]	3 [0.8]
Investigations	0	0	1 (0.9) [2.5]	0	3 [3.0]	4 [1.1]
Cardiac disorders	0	0	0	0	0	1 [0.3]
Eye disorders	0	0	0	0	0	1 [0.3]
Neoplasms benign, malignant, and unspecified <sup>c</sup>	0	0	0	0	0	1 [0.3]
Psychiatric disorders	0	0	0	0	0	1 [0.3]

*adj* adjusted, *All-bari-AD* participants who received any dose of baricitinib, *IR* incidence rate, *TEAE* treatment-emergent adverse event

<sup>a</sup>All baricitinib doses includes the baricitinib 1 mg, 2 mg, and 4 mg doses

<sup>b</sup>The preferred terms under the system organ class of skin and subcutaneous disorders were toxic skin eruption, dermatitis atopic, eczema, skin ulcer, dermatitis exfoliative generalized, rash, alopecia areata, angioedema, drug eruption, and pityriasis rosea

<sup>c</sup>Neoplasms comprised benign, malignant and unspecified, including cysts and polyps

tions did not increase in the 2-mg—4-mg extended and All-bari-AD datasets compared with the placebo-controlled dataset for both doses of baricitinib. In the placebo-controlled dataset, there were no serious infections with placebo and baricitinib 2 mg, whereas one participant (1.3%) had a serious infection with

baricitinib 4 mg (tonsillitis). No cases of tuberculosis, gastrointestinal perforations, or adverse cardiovascular events, including major adverse cardiovascular events, deep vein thrombosis, and pulmonary embolism, were reported.

Treatment-emergent adverse events are presented in detail in Table 3. The most common

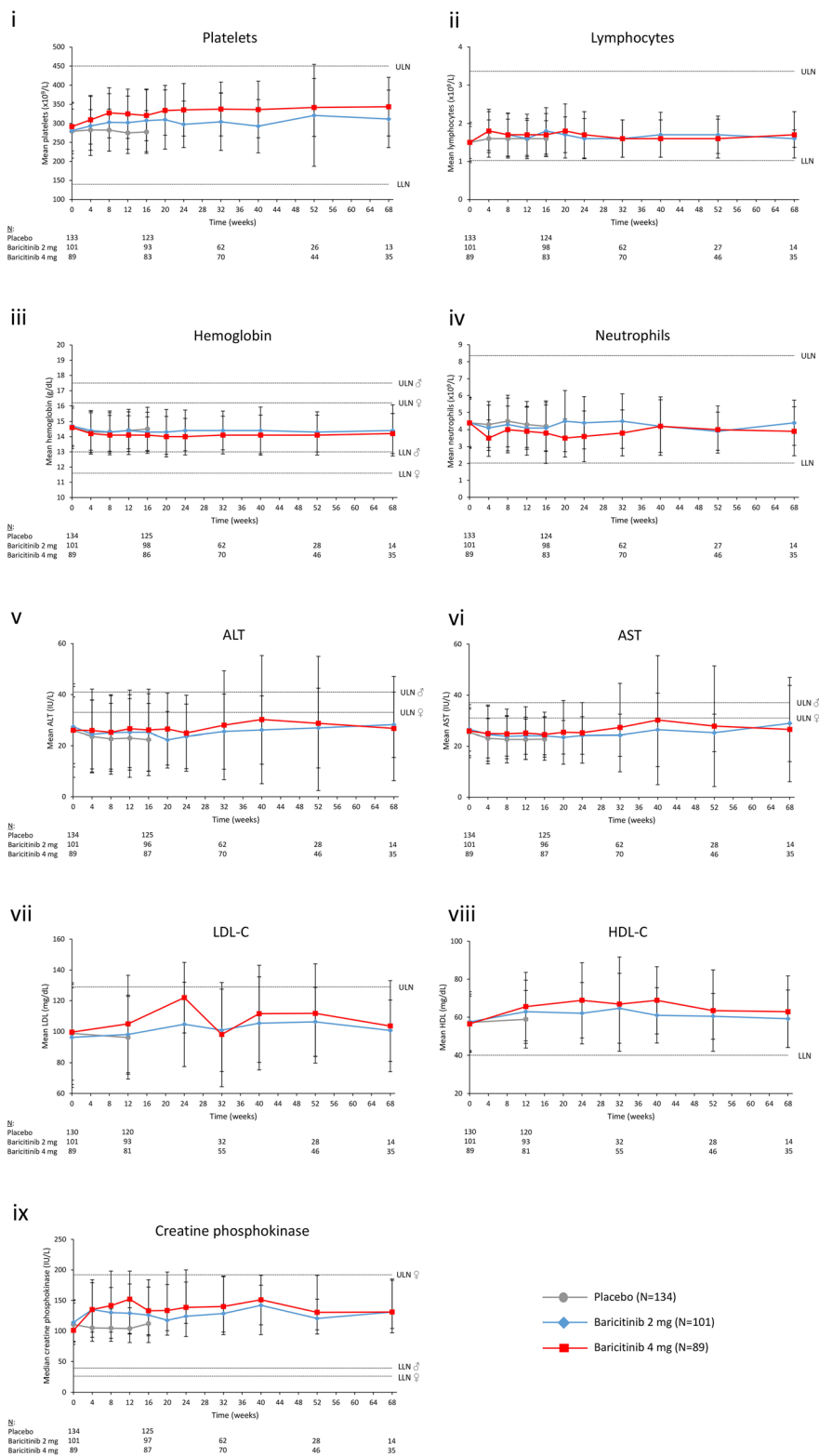


**Table 4** Changes in selected laboratory values and clinical chemistry in the Japanese subpopulation

Treatment-emergent changes, <i>n</i> / <i>NAR</i> (%)	Placebo-controlled (to week 16)			2-mg – 4-mg extended		All- <i>bari-AD</i> <sup>a</sup> , <i>N</i> = 341
	Placebo, <i>N</i> = 134	Baricitinib 2 mg, <i>N</i> = 101	Baricitinib 4 mg, <i>N</i> = 89	Baricitinib 2 mg, <i>N</i> = 101	Baricitinib 4 mg, <i>N</i> = 89	
LDL-C ≥ 130 mg/dL	5/105 (4.8)	12/90 (13.3)	14/73 (19.2)	16/90 (17.8)	22/73 (30.1)	69/278 (24.8)
HDL-C ≥ 60 mg/dL	16/71 (22.5)	15/62 (24.2)	17/49 (34.7)	21/62 (33.9)	20/49 (40.8)	67/186 (36.0)
Triglycerides ≥ 500 mg/dL	3/125 (2.4)	1/100 (1.0)	2/88 (2.3)	1/100 (1.0)	3/88 (3.4)	7/335 (2.1)
Creatine phosphokinase (U/L)						
> ULN	8/124 (6.5)	14/95 (14.7)	18/85 (21.2)	18/95 (18.9)	27/85 (31.8)	78/314 (24.8)
> 2.5 × ULN	2/132 (1.5)	2/99 (2.0)	2/87 (2.3)	3/99 (3.0)	6/87 (6.9)	20/334 (6.0)
> 5 × ULN	2/133 (1.5)	1/101 (1.0)	2/89 (2.2)	2/101 (2.0)	4/89 (4.5)	13/340 (3.8)
> 10 × ULN	1/134 (0.7)	1/101 (1.0)	0	2/101 (2.0)	1/89 (1.1)	7/340 (2.1)
Hemoglobin						
< LLN	9/126 (7.1)	7/98 (7.1)	12/84 (14.3)	11/98 (11.2)	18/84 (21.4)	44/312 (14.1)
< 10 mg/dL	0	0	1/89 (1.1)	1/100 (1.0)	1/89 (1.1)	3/339 (0.9)
< 8 mg/dL	0	0	0	0	0	0
Neutrophils < 1000 cells/mm <sup>3</sup>	0	0	0	0	1/89 (1.1)	1/340 (0.3)
Lymphocytes < 500 cells/mm <sup>3</sup>	0	0	2/89 (2.2)	0	2/89 (2.2)	2/340 (0.6)
Platelets > 600 billion/L	0	2/101 (2.0)	0	4/101 (4.0)	0	7/339 (2.1)
Patients with any postbaseline elevation in ALT, <i>n</i> / <i>N</i> (%)						
≥ 3 × ULN	0	0	0	0	2/89 (2.1)	4/340 (1.2)
≥ 5 × ULN	0	0	0	0	0	0
≥ 10 × ULN	0	0	0	0	0	0

*All-*bari-AD** participants who received any dose of baricitinib, *ALT* alanine aminotransferase, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *LLN* lower limit of normal, *NAR* number of participants at risk for the specified abnormality, *ULN* upper limit of normal

<sup>a</sup>All baricitinib doses includes the baricitinib 1 mg, 2 mg, and 4 mg doses



◀**Fig. 1** Values over time for platelets (i), lymphocytes (ii), hemoglobin (iii), neutrophils (iv), ALT (v), AST (vi), LDL-C (vii), HDL-C (viii), and creatine phosphokinase (ix) in the Japanese subpopulation. Data presented as mean  $\pm$  standard deviation, with the exception of creatine phosphokinase, which is presented as median  $\pm$  interquartile ratio. *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *LLN* lower limit of normal, *ULN* upper limit of normal

TEAE with baricitinib was nasopharyngitis in the placebo-controlled, the 2-mg–4-mg extended, and All-bari-AD datasets. The IRs for the most common TEAEs generally did not increase in the 2-mg–4-mg extended and All-bari-AD datasets compared with the placebo-controlled dataset.

There were seven permanent discontinuations of study drug due to AEs in the placebo-controlled dataset and 16 discontinuations in the All-bari-AD dataset (Table 2). Permanent discontinuations of study drug in the All-bari-AD dataset were most commonly due to AEs in the system organ classes of skin and subcutaneous tissue disorders (five participants), investigations (four participants; one with alanine aminotransferase increased, one with neutrophil count decreased, one with ultrasound abdomen abnormal, and one with white blood cell count increased), and infections and infestations (three participants).

### Laboratory Values and Clinical Chemistry in the Japanese Subpopulation

The most frequent treatment-emergent changes in laboratory values and clinical chemistry with baricitinib in participants in both the placebo-controlled and All-bari-AD datasets were high-density lipoprotein cholesterol (HDL-C)  $\geq$  60 mg/dL, low-density lipoprotein cholesterol (LDL-C)  $\geq$  130 mg/dL, and creatine phosphokinase greater than the upper limit of normal ( $>$  ULN) (Table 4).

Values over time for platelets, lymphocytes, hemoglobin, neutrophils, alanine aminotransferase, aspartate aminotransferase, LDL-C, HDL-

C, and creatine phosphokinase are shown in Fig. 1. Mean LDL-C increased through 24 weeks compared with baseline, most notably with the baricitinib 4 mg dose, and then steadily decreased to near baseline levels through 68 weeks. Both doses of baricitinib resulted in modest increases in median creatine phosphokinase up to 12 weeks, which then remained steady through 68 weeks. There was a dose-dependent increase in mean platelets over the first 8 weeks, which remained steady thereafter.

## DISCUSSION

A previous pooled analysis of safety data from eight global studies confirmed the established safety profile of baricitinib in participants with moderate-to-severe AD [10]. This pooled analysis builds on the previously published global findings and shows that the safety profile of baricitinib in participants with moderate-to-severe AD in the Japanese subpopulation is similar to that of the global study population.

The mean age of participants in the Japanese subpopulation was similar compared with the global study population (35.7 versus 36.4 years) [10]. Therefore, as safety information in patients with AD aged  $\geq$  75 years is limited compared with younger patients, this should be taken into consideration when choosing the dose of baricitinib for these patients. Compared with the global study population, a smaller proportion of the Japanese subpopulation was female (25.5% versus 39.3%) and had severe disease (43.5% versus 46.9%), the Eczema Area and Severity Index was higher (34.9 versus 31.1), and a greater proportion of participants had  $\geq$  1 year exposure to baricitinib (58.9% versus 41.9%) [10].

Similar to the global study population [10], the proportion of participants with TEAEs in the Japanese subpopulation was similar between the baricitinib 2 mg and 4 mg doses in the placebo-controlled dataset (Japanese subpopulation 50.5% and 58.4%, respectively; global study population 49.3% and 51.0%, respectively), and both doses were associated with a higher frequency of TEAEs than placebo [10]. The IRs for any TEAE were also similar for both

doses of baricitinib in the 2-mg—4-mg extended dataset (Japanese subpopulation 197.7 and 200.7, respectively; global study population 237.3 and 248.3, respectively) [10]. The most common TEAE for participants in the All-bari-AD dataset was nasopharyngitis for the Japanese subpopulation, which was consistent with the global study population [10]. Permanent discontinuations of study drug due to AEs were low for both the Japanese and global populations [10].

In the placebo-controlled dataset in the Japanese subpopulation, the proportion of participants with SAEs was similar in the placebo group compared with the baricitinib 4 mg group (1.9% versus 2.9%), and there were no SAEs with the baricitinib 2 mg dose. Furthermore, the proportion of participants within the Japanese subpopulation who experienced SAEs was similar compared with the global study population (1.4–2.3% for baricitinib versus 2.3% for placebo) in the placebo-controlled dataset [10]. The IR for SAEs in the All-bari-AD dataset was lower for the Japanese subpopulation (3.5) compared with the global study population (6.1) despite a greater proportion of Japanese participants having  $\geq 1$  year exposure to baricitinib compared with the global study population (58.9% versus 41.9%) [10]. However, this may have been due to differences in baseline demographics between the two populations, such as a lower proportion with severe disease (43.5% versus 46.9%) and prior systemic therapy with cyclosporine (17.8% versus 34.0%) for the Japanese subpopulation compared with the global study population [10]. There were no deaths in the Japanese subpopulation compared with one death in the global study population [10].

People with AD generally have an increased risk of cutaneous and noncutaneous bacterial and viral infections as a result of a defective skin barrier and immune system dysregulation [11]. Consequently, treatment-emergent infections were investigated as AESI. The proportion of participants with serious infections with baricitinib was similar compared with placebo in the Japanese subpopulation in the placebo-controlled dataset (baricitinib 2 mg: 0%; baricitinib 4 mg: 1.3%; placebo: 0%), and remained low

and similar over time compared with the global study population (1.3 versus 2.1) in the All-bari-AD dataset [10]. The most commonly reported infections in participants in the All-bari-AD dataset were the same for both the Japanese subpopulation and the global study population (nasopharyngitis and herpes simplex), indicating that the types of infections were similar for both populations [10].

Malignancies, cardiovascular AEs, gastrointestinal perforations, and ocular AEs were also investigated as AESI. The IRs for malignancies excluding nonmelanoma skin cancer in participants in the All-bari-AD dataset were 0.52 for the Japanese subpopulation and 0.2 for the global study population [10]. There were no major adverse cardiovascular outcomes or venous thromboembolisms in the Japanese subpopulation compared with an IR of 0.09 for both event types in the global study population [10]. There were no gastrointestinal perforations for both the Japanese and global populations [10]. The IR for conjunctival disorders was 1.9 in participants who received any baricitinib dose in the Japanese subpopulation compared with 4.3 in the global study population [10]. Overall, these findings indicate that the incidence and type of AESI were low and similar for both the Japanese and global populations.

Treatment-emergent changes in laboratory values, including LDL-C  $\geq 130$  mg/dL (24.8% versus 21.8%), triglycerides  $\geq 500$  mg/dL (2.1% versus 1.0%), creatine phosphokinase ( $>$  ULN, 24.8% versus 28.8%), and alanine aminotransferase  $\geq 3 \times$  ULN (1.2% versus 1.6%), were similar for the Japanese and global populations for participants in the All-bari-AD dataset, and are known adverse drug reactions for baricitinib [10].

The safety profile of baricitinib in RA has been investigated in an analysis of 514 Japanese participants with RA from five phase 2 and phase 3 studies, and one long-term extension study [12]. In this analysis, the IRs for several TEAEs, including serious infections and herpes zoster, appeared higher than in the Japanese subpopulation in the All-bari-AD dataset in this study [12], and suggest that AEs may be less frequent in Japanese people with AD compared with RA. These differences in IRs are likely

related to the older age, greater disease severity, higher concomitant use of systemic corticosteroids and/or immunosuppressant drugs, and associated greater susceptibility for these AEs in people with RA compared with people with AD.

Other treatments for AD, including the JAK inhibitors abrocitinib and upadacitinib, and the interleukin (IL)-4 and IL-13 inhibitor dupilumab, have been approved in Japan for the treatment of AD. Unlike baricitinib, dupilumab has not been evaluated in people with RA, who are generally older and more likely to be taking concomitant systemic corticosteroids and other immunosuppressant drugs, particularly those with a higher risk for major adverse cardiovascular events, venous thromboembolism, malignancies, and serious infections. The Japanese Dermatological Association updated their Guidelines for the Management of Atopic Dermatitis in December 2021. In recognition of its benefits, baricitinib has been added to the recommended treatment algorithm, along with dupilumab and delgocitinib [13].

There are several limitations to this study. For instance, the IRs can be compared with other studies for context only, and inferences cannot be made as study and treatment are confounded because of the possibility of rescue treatment in nonresponders and downtitration of responders, among other factors. Moreover, risk over time can change owing to reasons other than treatment exposure. There are also inherent limitations to observational data. An additional limitation is that a longer treatment duration is required to evaluate malignancies and major adverse cardiovascular events. Another limitation is that total exposure to baricitinib in the Japanese subpopulation was relatively low compared with the global study population [10], which was consequently a more reliable source of safety data, particularly for rare events. In addition, the results may be prospective, which could limit the applicability of the study to real-world clinical practice.

## CONCLUSIONS

This pooled analysis of safety data for baricitinib in moderate-to-severe AD from six placebo-

controlled clinical studies and one long-term extension study with exposure up to 2 years supports the established safety profile of baricitinib in participants with moderate-to-severe AD from Japan.

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**Data Availability.** Eli Lilly provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the US and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, and blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at [www.vivli.org](http://www.vivli.org).

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