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ORIGINAL RESEARCH ARTICLE

Extended Safety Analysis of Baricitinib 2 mg in Adult Patients with Atopic Dermatitis: An Integrated Analysis from Eight Randomized Clinical Trials

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Abstract

Background Baricitinib, a selective Janus kinase 1/Janus kinase 2 inhibitor, is indicated in the European Union and Japan for the treatment of moderate-to-severe atopic dermatitis (AD) in adults who are candidates for systemic therapy.

Objective The objective of this study was to evaluate the safety of baricitinib 2 mg in the AD clinical program.

Methods Six double-blind, randomized, placebo-controlled studies, and two long-term extension studies were summarized in two datasets. Placebo comparison was based on six 16-week studies with baricitinib 2 mg. All-bari-2-mg-AD included patients who received baricitinib 2 mg at any time during the eight studies.

Results In total, 1598 patients received once-daily baricitinib 2 mg for 1434.2 patient-years of exposure (median 330 days/maximum 2.4 years). Treatment-emergent adverse events were higher for baricitinib 2 mg (57.9%) vs placebo (51.6%). Serious adverse events, serious infections, and opportunistic infections were low in frequency and similar between baricitinib 2 mg and placebo. There were no malignancies, gastrointestinal perforations, or major adverse cardiovascular events with baricitinib 2 mg in the placebo-controlled period. Herpes simplex (cluster) was higher for baricitinib 2 mg (3.8%) vs placebo (2.8%); rates decreased with extended 2 mg exposure. In All-bari-2-mg-AD, there were five malignancies other than non-melanoma skin cancer, two major adverse cardiovascular events, one peripheral venous thrombosis, one arterial thrombosis, and no pulmonary embolisms, deep vein thromboses, or deaths.

Conclusions This integrated analysis in patients with moderate-to-severe AD confirms the established safety profile of baricitinib 2 mg. Longer exposure to treatment is required to evaluate risks of malignancies and major adverse cardiovascular events.

Clinical Trial registration ClinicalTrials.gov identifiers: NCT02576938 (first posted 15 October, 2015); NCT03334396 (7 November, 2017); NCT03334422 (7 November, 2017); NCT03428100 (9 February, 2018); NCT03435081 (15 February, 2018); NCT03733301 (7 November, 2018); NCT03334435 (7 November, 2017); NCT03559270 (18 June, 2018).

Plain Language Summary

Baricitinib is a medication that helps an overactive immune system adjust itself, leading to improvements in the inflammatory condition atopic dermatitis. Baricitinib is approved for patients with moderate-to-severe atopic dermatitis in 40 countries. Because it works with the immune system, it is important to understand the safety of

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baricitinib. Safety information was collected from eight studies and analyzed in two datasets. The first dataset compared the safety of baricitinib 2 mg with placebo in six 16-week studies in which neither patient nor physician knew whether they were taking baricitinib or placebo. The second dataset included an additional two extension studies and examined the safety of baricitinib in all patients receiving at least one dose of baricitinib 2 mg. Patients took baricitinib 2 mg for a maximum of 2.4 years, with a median time of 330 days. In the first dataset, adverse events were higher for baricitinib 2 mg (57.9%) than placebo (51.6%). Serious adverse events, serious infections, and opportunistic infections were low in number and similar for patients taking baricitinib 2 mg or placebo. Herpes simplex infections were more frequent in patients taking baricitinib 2 mg (3.8%) than in those taking placebo (2.8%), but rates in those taking baricitinib 2 mg decreased with a longer treatment duration. There were no occurrences of cancer, gastrointestinal perforations, or major adverse cardiovascular events. In the second dataset, there were five reports of cancer other than non-melanoma skin cancer, two major adverse cardiovascular events, one peripheral venous thrombosis, one arterial thrombosis, and no pulmonary embolisms, deep vein thromboses, or deaths. Longer treatment with baricitinib is required to better understand the risks of developing cancer or major adverse cardiovascular events. This analysis of safety in patients with moderate-to-severe atopic dermatitis is consistent with the safety reported previously for baricitinib 2 mg.

Key Points

This long-term safety analysis confirms the established safety profile of baricitinib 2 mg in atopic dermatitis.

There was no further increase in rates for adverse events, serious adverse events, or serious infections with long-term baricitinib 2-mg therapy as compared to rates with baricitinib 2 mg in the placebo-controlled period. Baricitinib 2 mg showed no increase in anemia, neutropenia, lymphopenia, or elevated liver enzymes compared to placebo.

There was an increase in cases of herpes simplex with baricitinib 2 mg compared with placebo, with lower rates for prolonged baricitinib 2 mg exposure. There was no increase in the risk of eczema herpeticum with baricitinib 2 mg.

A longer treatment duration is needed to appropriately assess the risk of malignancies and cardiovascular events.

1 Introduction

Atopic dermatitis (AD) is a common, chronic, pruritic inflammatory skin disease characterized by dysregulated immune responses, skin barrier dysfunction, and increased susceptibility to microbial infection [1–6]. Many pro-inflammatory cytokines implicated in AD pathogenesis are dependent on Janus kinases (JAKs; JAK1, JAK2, and tyrosine kinase 2) for intracellular signaling [7–9]. Baricitinib, an oral selective JAK1/JAK2 inhibitor [10], is predicted to inhibit several of these cytokines, including thymic stromal lymphopoietin, interleukin (IL)-4, IL-5, IL-13, IL-22, and IL-31 [7–9]. Baricitinib is indicated in the European Union and Japan and being evaluated in the USA and other countries for the treatment of moderate-to-severe AD in adult patients who are candidates for systemic therapy, and is in late-stage development for adults with alopecia areata [11, 12]. Baricitinib is also approved for the treatment of adults with moderately-to-severely active rheumatoid arthritis (RA). While a safety profile for JAK inhibition in RA has been well characterized [13, 14], JAK inhibitors (JAKis) represent a new class of medication for dermatologic disease, raising the need to further elucidate the emerging safety profile of JAKis in AD.

In multiple randomized, placebo-controlled, phase II and phase III clinical trials in adults with moderate-to-severe AD, baricitinib as monotherapy or in combination with topical corticosteroids improved clinical signs and symptoms of AD [15–18]. An integrated safety analysis of baricitinib clinical trials, including two ongoing long-term extension (LTE) trials with exposure up to 2 years, informs the safety profile of baricitinib in AD [19]; the objective of this integrated analysis was to further evaluate the safety of once-daily baricitinib 2 mg from these trials with LTE exposure up to 2.4 years.

2 Methods

2.1 Study Designs and Patients

Data are presented from six randomized double-blind trials (phase II: NCT02576938; phase III: NCT03334396 [BREEZE-AD1], NCT03334422 [BREEZE-AD2],

NCT03428100 [BREEZE-AD4] [ongoing], NCT03435081 [BREEZE-AD5] [ongoing], and NCT03733301 [BREEZE-AD7]), one ongoing randomized, double-blind LTE (NCT03334435 [BREEZE-AD3]), and one ongoing open-label LTE (NCT03559270 [BREEZE-AD6]), with follow-up to 2.4 years. Study design and key eligibility criteria are described in Table S1 and the Methods in the Electronic Supplementary Material (ESM). Trials were conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines and approved by the ethics committee or institutional review board of each center. All patients provided written informed consent.

2.2 Analysis Sets

Two integrated datasets were analyzed:

1. The 'placebo-controlled' dataset assessed the safety profile of baricitinib 2 mg vs placebo during the 16-week, placebo-controlled period for patients in one phase II and five phase III trials.
2. The 'All-bari-2-mg-AD' dataset provided estimated incident rates (IRs) of adverse events (AEs) for all patients who received one or more doses of baricitinib 2 mg from all periods in any of the eight trials.

2.3 Safety Outcomes

The safety analysis included treatment-emergent AEs (TEAEs), AEs leading to temporary interruption or permanent discontinuation of the study drug, serious AEs (SAEs), death, AEs of special interest, and abnormal laboratory changes (detailed in Table S2 of the ESM). Cluster analyses grouping preferred terms (PTs) and terms associated with related clinical disease presentations were used for some AEs as described in Table S2 of the ESM.

2.4 Statistical Analysis

For the placebo-controlled dataset, adjusted percentages and adjusted IRs were calculated for AEs to provide appropriate direct comparison across treatment groups because the randomization ratio of treatment groups differed across studies. Adjusted percentages were derived using study weights based on sample size per study. Adjusted IRs per 100 patient-years at risk of observation time, censored at event, were derived using study weights based on total patient-years of exposure per study. For All-bari-2-mg-AD, IRs were calculated as the number of patients with an event per 100 patient-years at risk of observation time, censored at event.

3 Results

3.1 Patients

Baseline patient demographics and disease activity were overall balanced between baricitinib 2 mg and placebo (Table 1). In All-bari-2-mg-AD, 1598 patients received baricitinib 2 mg, with 1434.2 patient-years of exposure; 729 (45.6%) and 34 (2.1%) were treated for ≥ 1 year or ≥ 2 years, respectively, with a median exposure of 330 days and maximum exposure of 869 days (2.4 years) (Table 2).

3.2 TEAEs

A higher proportion of patients reported one or more TEAE with baricitinib 2 mg (57.9%) compared with placebo (51.6%) (Table 2); most were mild (baricitinib 2 mg 32.8%, placebo 29.9%) or moderate (baricitinib 2 mg 22.2%, placebo 18.3%) in severity. The most frequently reported (≥ 2% in any treatment group) TEAEs in the placebo-controlled dataset were nasopharyngitis, headache, upper respiratory tract infection, nausea, diarrhea, and herpes simplex (Table 3). The frequency of SAEs was lower with baricitinib 2 mg (1.6%, IR = 5.2) compared with placebo (2.7%, IR = 9.2) (Table 2); the most common SAEs reported in All-bari-2-mg-AD were in the Medical Dictionary for Regulatory Activities (MedDRA) system organ classes Skin and subcutaneous tissue disorders (the most common PT was dermatitis atopic, $n = 12$, IR = 0.8) and Infections and infestations (the most common PTs are described in Sect. 3.3.1). The IR for SAEs with long-term baricitinib 2 mg exposure was similar to the IR observed during the placebo-controlled period, at 4.7 (All-bari-2-mg-AD, Table 2). No deaths were reported.

A similar proportion of patients discontinued the study drug because of AEs in the baricitinib 2 mg group (1.9%, IR = 6.2) and the placebo group (1.8%, IR = 6.1); the All-bari-2-mg-AD IR was 3.8 (Table 2). In All-bari-2-mg-AD, the most common MedDRA system organ class for permanent discontinuation was Skin and subcutaneous disorders (n = 12/56, 21.4%) (Table 3) with 50% of these events reported as worsening of dermatitis atopic. A greater proportion of patients experienced temporary interruptions of the study drug because of AEs with baricitinib 2 mg (3.5%, IR = 12.0) compared with placebo (2.0%, IR = 7.0); the All-bari-2-mg-AD IR was 8.4 (Table 2). In All-bari-2-mg-AD, the most common MedDRA system organ classes for temporary interruptions was Infections and infestations (n = 72/118, 61%); the most frequently reported PTs were herpes zoster ($n = 15$), herpes simplex ($n = 7$), and upper respiratory tract infection ($n = 6$).

Table 1 Baseline demographics and disease characteristics

	Placebo-controlled (to week 16)		All-bari-2-mg-AD
	Placebo ($N = 889$)	Baricitinib 2 mg ($N = 721$)	All-bari-2-mg-AD ($N = 1598$)
Age (years)	36.3 (13.7)	36.7 (13.9)	36.7 (14.2)
Female, *n* (%)	365 (41.1)	282 (39.1)	662 (41.4)
Duration since AD diagnosis (years)	24.6 (15.0)	24.8 (14.6)	24.7 (15.1)
BMI (kg/m^2)	25.7 (5.4)	26.3 (6.0)	26.1 (5.6)
Geographic region, *n* (%)			
Central/South America and Mexico	76 (8.5)	56 (7.8)	177 (11.1)
USA/Canada (including Puerto Rico)	187 (21.0)	176 (24.4)	405 (25.3)
Asia (excluding Japan)	99 (11.1)	62 (8.6)	135 (8.4)
Japan	134 (15.1)	101 (14.0)	163 (10.2)
Europe	365 (41.1)	297 (41.2)	637 (39.9)
Rest of world	28 (3.1)	29 (4.0)	81 (5.1)
Prior topical therapy, *n* (%)			
Topical corticosteroids	783 (88.1)	632 (87.7)	1437 (89.9)
Topical calcineurin inhibitor	461/809 (57.0)	358/625 (57.3)	749/1495 (50.1)
Prior systemic therapy, *n* (%)			
Cyclosporine	265/800 (33.1)	271/628 (43.2)	450/1551 (29.0)
vIGA-AD score of 4[a], *n* (%)	384/840 (45.7)	318/684 (46.5)	615/1314 (46.8)
EASI[b]	30.7 (12.5)	30.3 (12.9)	30.4 (12.8)
Percentage body surface area affected	49.5 (23.0)	48.7 (23.3)	48.6 (23.2)
Itch NRS[c]	6.9 (2.1)	6.8 (2.2)	6.9 (2.1)

Data are mean (SD) unless otherwise indicated

AD atopic dermatitis, *BMI* body mass index, *EASI* Eczema Area and Severity Index, *N* number of patients in the analysis set, *n* number of patients in the specified category, *NRS* Numeric Rating Scale, *SD* standard deviation, *vIGA-AD* validated Investigator Global Assessment for Atopic Dermatitis

[a]vIGA-AD measures the investigator global assessment of disease severity based on a static 5-point scale from 0 (clear skin) to 4 (severe disease)

[b]EASI scores range from 0 to 72, with higher scores indicating greater severity

[c]Itch NRS ranges from 0 (no itch) to 10 (worst itch imaginable)

3.3 AEs of Special Interest

3.3.1 Infections

There was a greater proportion of patients with one or more treatment-emergent infections with baricitinib 2 mg (34.4%) compared with placebo (28.4%). Serious infections were low in frequency and similar with baricitinib 2 mg (0.5%, IR = 1.4) and placebo (0.7%, IR = 2.5). In All-bari-2-mg-AD, the serious infection IR was 1.5; the most common serious infections were cellulitis ($n = 3$, IR = 0.2), eczema herpeticum (EH) ($n = 3$, IR = 0.2), and pneumonia ($n = 3$, IR = 0.2). The proportion of patients developing skin infections requiring antibiotic treatment was similar with baricitinib 2 mg (5.5%, IR = 19.1) and placebo (5.4%, IR = 19.0); the All-bari-2-mg-AD IR was 2.6 (Table 2).

A greater proportion of patients reported herpes simplex (evaluated as a cluster) with baricitinib 2 mg (3.8%, IR = 13.2) compared with placebo (2.8%, IR = 9.8); the two most common PTs were herpes simplex (baricitinib 2 mg: $n = 13$, 2.0%, IR = 7.1; placebo: $n = 8$, 0.9%, IR = 3.2) and oral herpes (baricitinib 2 mg: $n = 12$, 1.5%, IR = 5.0; placebo: $n = 10$, 1.3%, IR = 4.5). In All-bari-2-mg-AD, the herpes simplex cluster IR was 7.7 ($n = 108$); most were mild or moderate in severity, did not result in permanent discontinuation from the study drug, and the most common PTs were oral herpes ($n = 58$, IR = 4.0), herpes simplex ($n = 38$, IR = 2.6), and EH ($n = 15$, IR = 1.0). The median days to onset for the herpes simplex cluster in All-bari-2-mg-AD was 166 (range = 2–701); 30 patients (27.8%) had recurrent herpes simplex infections. In the placebo-controlled dataset, EH (evaluated as a cluster) was reported in four patients treated with placebo (0.4%, IR = 1.3) [reported as EH] and one patient with baricitinib 2 mg (0.2%, IR = 0.7) [reported as Kaposi's varicelliform eruption]. In All-bari-2-mg-AD, the EH cluster IR was 1.4 ($n = 20$); 15 patients reported the PT EH (IR = 1.0) and five patients reported the PT Kaposi's varicelliform eruption (IR = 0.3) (Table 2). Of the 20 EH cases reported (cluster), nine were reported as mild and 12

Table 2 Overview of safety measures including exposure, treatment-emergent AEs, and AEs of special interest

	Placebo-controlled (to week 16)		All-bari-2-mg-AD
	Placebo ($N = 889$)	Baricitinib 2 mg ($N = 721$)	All-bari-2-mg-AD ($N = 1598$)
Exposure			
Total patient-years	252.7	210.6	1434.2
No. of patients with ≥ 52 weeks[a], *n* (%)	–	–	729 (45.6)
No. of patients with ≥ 104 weeks, *n* (%)	–	–	34 (2.1)
Median duration, days	113	113	330
Maximum exposure, days	168	128	869
AEs, *n* (%) [IR][b]			
Any treatment-emergent AE	460 (51.6) [277.6]	421 (57.9) [325.5]	1032 [159.6]
Serious AE	24 (2.7) [9.2]	12 (1.6) [5.2]	68 [4.7]
Interruption of the study drug because of AE	18 (2.0) [7.0]	28 (3.5) [12.0]	118 [8.4]
Discontinuation of the study drug because of AE	17 (1.8) [6.1]	14 (1.9) [6.2]	56 [3.8]
Death	0	0	0
Infections, *n* (%) [IR][b]			
Treatment-emergent infections	252 (28.4) [117.0]	251 (34.4) [146.0]	732 [80.6]
Serious infections	6 (0.7) [2.5]	4 (0.5) [1.4]	22 [1.5]
Skin infections requiring antibiotic treatment	46 (5.4) [19.0]	37 (5.5) [19.1]	37 [2.6]
Herpes simplex cluster	23 (2.8) [9.8]	27 (3.8) [13.2]	108 [7.7]
Herpes simplex	8 (0.9) [3.2]	13 (2.0) [7.1]	38 [2.6]
Oral herpes	10 (1.3) [4.5]	12 (1.5) [5.0]	58 [4.0]
Kaposi's varicelliform eruption	0	1 (0.2) [0.7]	5 [0.3]
Genital herpes simplex	0	1 (0.1) [0.3]	2 [0.1]
Genital herpes	1 (0.2) [0.7]	0	2 [0.1]
Ophthalmic herpes simplex	0	0	3 [0.2]
Herpes opthalmic	0	0	2 [0.1]
Eczema herpeticum	4 (0.4) [1.3]	0	15 [1.0]
Eczema herpeticum cluster	4 (0.4) [1.3]	1 (0.2) [0.7]	20 [1.4]
Eczema herpeticum	4 (0.4) [1.3]	0	15 [1.0]
Kaposi's varicelliform eruption	0	1 (0.2) [0.7]	5 [0.3]
Herpes zoster	3 (0.3) [1.0]	6 (0.8) [2.7]	30 [2.1]
Tuberculosis	0	0	0
Opportunistic infection excluding tuberculosis[c]	1 (0.1) [0.4]	1 (0.1) [0.3]	3 [0.2]
Malignancy, *n* (%) [IR][b]			
Malignancies other than NMSC	2 (0.2) [0.66]	0	5 [0.34]
NMSC	1 (0.2) [0.68]	0	4 [0.27]
Cardiovascular AEs of special interest, *n* (%) [IR][b]			
MACE[d,e]	0	0	2/1561 [0.14]
DVT[d]	0	0	0
PE[d]	0	0	0
Peripheral venous thrombosis[d]	0	0	1/1561 [0.07]
Arterial thromboembolic event[c]	0	0	1 [0.07]
Gastrointestinal disorder, *n* (%) [IR][b]			
Gastrointestinal perforation	0	0	0
Ocular AEs, *n* (%) [IR][b]			
Conjunctival disorders	18 (2.4) [8.7]	15 (2.0) [6.8]	51 [3.5]

AD atopic dermatitis, *AE* adverse event, *DVT* deep vein thrombosis, *IR* incidence rate, *MACE* major adverse cardiovascular event, *N* number of patients in the analysis set, *n* number of patients in the specified category, *NMSC* non-melanoma skin cancer, *PE* pulmonary embolism

[a]According to the week 52 minimum protocol window of 4 days = 360 days

[b]For the placebo-controlled dataset, study-size adjusted percentages and IRs are shown

[c]Medically reviewed by a blinded internal committee

Table 2 (continued)

[d]All AEs suggestive of a possible MACE, DVT, PE, or other peripheral venous thrombosis were adjudicated in a blinded manner by an experienced external independent clinical event committee. Adjudication determined whether these AEs qualified as MACE, DVT, PE, or other peripheral venous thrombosis based on evaluations of case descriptions and any diagnostic tests available. AEs meeting the adjudication committee definitions for these specific events were considered positively adjudicated. A positively adjudicated event provides additional diagnostic confirmation but does not assess a causal relationship to the study drug

[e]A MACE was defined as cardiovascular death, myocardial infarction, or stroke as adjudicated by an external independent clinical event committee

Table 3 Adverse event details

	Placebo-controlled (to week 16)[a]		All-bari-2-mg-AD
	Placebo ($N = 889$) [PYE = 252.7] *n* (adj %) [adj IR]	Baricitinib 2 mg ($N = 721$) [PYE = 210.6] *n* (adj %) [adj IR]	All-bari-2-mg-AD ($N = 1598$) [PYE = 1434.2] *n* [IR]
Treatment-emergent adverse event by preferred term with frequency of at least 2% in any treatment group in the placebo-controlled dataset			
Nasopharyngitis	93 (10.6) [39.0]	74 (10.3) [36.9]	231 [17.8]
Headache	30 (3.5) [12.7]	40 (6.3) [22.3]	96 [6.8]
Upper respiratory tract infection	23 (2.4) [8.5]	34 (4.5) [15.4]	104 [7.4]
Nausea	11 (1.1) [3.9]	19 (2.3) [7.8]	29 [2.0]
Diarrhea	17 (2.0) [7.0]	16 (2.0) [6.7]	35 [2.4]
Herpes simplex	8 (0.9) [3.2]	13 (2.0) [7.1]	38 [2.6]
Permanent discontinuation of the study drug because of adverse event by system organ class			
Skin and subcutaneous tissue disorders[b]	4 (0.4) [1.3]	2 (0.2) [0.7]	12 [0.8]
Infections and infestations	3 (0.3) [1.1]	2 (0.3) [1.0]	9 [0.6]
Investigations	2 (0.3) [1.1]	2 (0.3) [1.0]	6 [0.4]
Nervous system disorders	2 (0.2) [0.7]	2 (0.2) [0.8]	4 [0.3]
Blood and lymphatic system disorders	3 (0.3) [0.9]	1 (0.1) [0.4]	1 [0.1]
Congenital, familial, and genetic disorders	0	1 (0.1) [0.4]	1 [0.1]
Eye disorders	0	1 (0.1) [0.7]	1 [0.1]
Gastrointestinal disorders	1 (0.1) [0.4]	1 (0.1) [0.3]	5 [0.3]
General disorders and administration-site conditions	0	1 (0.1) [0.3]	4 [0.3]
Psychiatric disorders	0	1 (0.2) [0.7]	1 [0.1]
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	2 (0.2) [0.7]	0	4 [0.3]
Renal and urinary disorders	0	0	1 [0.1]
Respiratory, thoracic, and mediastinal disorders	0	0	1 [0.1]
Cardiac disorders	0	0	2 [0.1]
Injury, poisoning, and procedural complications	0	0	2 [0.1]
Musculoskeletal and connective tissue disorders	0	0	1 [0.1]
Vascular disorders	0	0	1 [0.1]

AD atopic dermatitis, *IR* incidence rate, *N* number of patients in the analysis set, *n* number of patients in the specified category, *PYE* patient-years of exposure

[a]For the placebo-controlled dataset, study-size adjusted percentages and IRs are shown

[b]Events reported included the preferred terms alopecia areata, angioedema, dermatitis atopic, dermatitis exfoliative, dermatitis exfoliative generalized, eczema, pityriasis rosea, rash, and rosacea

had herpes infection involving 2% body surface area (BSA) or less.

Herpes zoster (HZ) events were reported more frequently with baricitinib 2 mg ($n = 6$, 0.8%, IR = 2.7) compared with placebo ($n = 3$, 0.3%, IR = 1.0) (Table 2). In All-bari-2-mg-AD, the HZ IR was 2.1 ($n = 30$); two events were reported as severe and none were reported as SAEs or resulted in permanent discontinuation from the study drug.

There were no reports of tuberculosis. Opportunistic infections were infrequent with no differences between baricitinib 2 mg (IR = 0.3) and placebo (IR = 0.4) (Table 2); there was one toxoplasma eye infection (placebo) and one multidermatomal HZ (baricitinib 2 mg). In All-bari-2-mg-AD, there were three opportunistic infections (IR = 0.2) (Table 2), including the one multidermatomal HZ, one recurrent HZ, and one ophthalmic herpes simplex.

3.3.2 Cardiovascular Events

There were no reports of major adverse cardiovascular events (MACE) in the placebo-controlled dataset. In All-bari-2-mg-AD, two patients had positively adjudicated MACE (IR = 0.14) (Table 2). One patient had a myocardial infarction and had risk factors including age, history of smoking, hypertension, obesity, high cholesterol, and pre-existing RA. The other patient was diagnosed with a ruptured cerebral aneurysm that was positively adjudicated as a hemorrhagic stroke that was not considered related to the study drug by the investigator.

There were no positively adjudicated pulmonary embolisms (PE) or deep vein thromboses (DVT). In All-bari-2-mg-AD, one patient developed a peripheral venous thrombosis after 40 weeks of baricitinib 2 mg treatment (IR = 0.07). The patient was later diagnosed with a genetic predisposition to thrombotic events (heterozygous Factor V-Leiden mutation). One patient in All-bari-2-mg-AD with a history of peripheral arterial occlusive disease had an arterial bypass occlusion (IR = 0.07) (Table 2).

3.3.3 Malignancies

No malignancies were reported with baricitinib 2 mg in the placebo-controlled dataset; there were two malignancies other than non-melanoma skin cancer (NMSC) in the placebo group (IR = 0.66), including one breast cancer and one papillary thyroid cancer, in addition to one NMSC (Bowen's disease) [IR = 0.68]. In All-bari-2-mg-AD, there were five malignancies other than NMSC (IR = 0.34), including one patient each with B-cell lymphoma (symptoms started prior to baricitinib treatment), diffuse large B-cell lymphoma, and rectal cancer, and two patients with prostate cancer; there were four NMSCs (all basal cell carcinoma) [IR = 0.27] (Table 2). The median days to onset for all malignancies including NMSC in All-bari-2-mg-AD was 261 (range = 96–629).

3.3.4 Gastrointestinal Disorders

There were no reports of gastrointestinal perforations (Table 2).

3.3.5 Conjunctival Disorders

The proportion of patients who reported conjunctival disorders within the standardized MedDRA queries cluster was similar with baricitinib 2 mg (2.0%, IR = 6.8) and placebo (2.4%, IR = 8.7); the All-bari-2-mg-AD IR was 3.5 (n = 51) (Table 2). The most common PTs reported in the cluster were conjunctivitis (n = 25, 49.0% of conjunctival disorders in All-bari-2-mg-AD) and conjunctivitis allergic (n = 14, 27.5%) [Table S3].

3.3.6 Laboratory Evaluation

Changes in selected laboratory analytes are shown in Table 4, including Common Terminology Criteria for Adverse Events (CTCAE) Grades and corresponding laboratory values. There were elevations in serum creatine phosphokinase with baricitinib 2 mg compared with placebo, with most increases being CTCAE Grade ≥ 1 (baricitinib 2 mg 19.6%, placebo 10.7%) and Grade ≥ 2 (baricitinib 2 mg 4.7%, placebo 3.0%), and few Grade ≥ 3 (baricitinib 2 mg 2.3%, placebo 1.8%); elevations were mostly asymptomatic (myalgia reported for one patient on placebo and two patients on baricitinib 2 mg), and there were no cases of rhabdomyolysis. There were no CTCAE Grade ≥ 3 changes in hemoglobin in the analysis. Few patients had CTCAE Grade ≥ 3 neutrophil changes (0.1% [1/707] for baricitinib 2 mg, none for placebo) and Grade ≥ 3 lymphocyte changes (0.1% [1/707] for baricitinib 2 mg, 0.2% [2/868] for placebo). A higher proportion of patients had treatment-emergent platelet increases > 600 billions/L with baricitinib 2 mg (1.1%) vs placebo (0%); increases were not related to thromboembolic events. There was a greater proportion of patients who had categorical increases in high-density lipoprotein (≥ 1.55 mmol/L; baricitinib 2 mg 21.0%, placebo 13.9%) and low-density lipoprotein (≥ 3.36 mmol/L; baricitinib 2 mg 11.9%, placebo 6.4%) with baricitinib 2 mg compared with placebo; increases were not related to MACE or cardiovascular events. Few patients had increases in triglycerides (≥ 5.65 mmol/L; baricitinib 2 mg 0.6%, placebo 1.0%). Increases in alanine aminotransferase or aspartate aminotransferase ≥ 3× or ≥ 5× the upper limit of normal were infrequent and numerically fewer for baricitinib 2 mg than placebo; one patient in All-bari-2-mg-AD with a history of alcohol abuse and seizure due to withdrawal had alanine aminotransferase ≥ 10× upper limit of normal (Table 4). Selected laboratory analytes over time are described in the Results and Fig. S1 of the ESM.

Table 4 Changes in selected laboratory analytes

	Placebo-controlled (to week 16)		All-bari-2-mg-AD
	Placebo ($N = 889$)	Baricitinib 2 mg ($N = 721$)	All-bari-2-mg-AD ($N = 1598$)
Creatinine phosphokinase			
Increase to ≥ Grade 1 (> ULN and ≤ 2.5× ULN)	84/783 (10.7)	125/638 (19.6)	314/1314 (23.9)
Increase to ≥ Grade 2 (> 2.5× ULN and ≤ 5× ULN)	26/856 (3.0)	33/697 (4.7)	99/1492 (6.6)
Increase to ≥ Grade 3 (> 5× ULN and ≤ 10× ULN)	16/865 (1.8)	16/703 (2.3)	48/1520 (3.2)
Increase to ≥ Grade 4 (> 10× ULN)	10/869 (1.2)	8/706 (1.1)	26/1534 (1.7)
Hemoglobin			
Increase to ≥ Grade 1 (< 7.27 mmol (Fe)/L [female]/8.18 mmol (Fe)/L [male] and ≥ 6.2 mmol (Fe)/L)	38/818 (4.6)	42/659 (6.4)	104/1420 (7.3)
Increase to ≥ Grade 2 (< 6.2 mmol (Fe)/L and ≥ 4.9 mmol (Fe)/L)	4/870 (0.5)	3/706 (0.4)	13/1540 (0.8)
Increase to ≥ Grade 3 (< 4.9 mmol (Fe)/L and ≥ 4.0 mmol (Fe)/L)	0	0	0
Neutrophils			
Increase to ≥ Grade 3 (< 1.0 billion/L and ≥ 0.5 billion/L)	0	1/707 (0.1)	2/1542 (0.1)
Lymphocytes			
Increase to ≥ Grade 3 (< 0.5 billion/L and ≥ 0.2 billion/L)	2/868 (0.2)	1/707 (0.1)	8/1542 (0.5)
Platelets			
Thrombocytosis ≤ 600 billions/L to > 600 billions/L	0	8/706 (1.1)	15/1538 (1.0)
LDL cholesterol			
Increase to borderline high (≥ 3.36 mmol/L and < 4.14 mmol/L), high (≥ 4.14 mmol/L and < 4.91 mmol/L), or very high (≥ 4.91 mmol/L)	41/643 (6.4)	64/540 (11.9)	229/1154 (19.8)
HDL cholesterol			
Increase to high (≥ 1.55 mmol/L)	73/524 (13.9)	92/438 (21.0)	254/921 (27.6)
Triglycerides			
Increase to very high (≥ 5.65 mmol/L)	8/789 (1.0)	4/632 (0.6)	12/1415 (0.8)
Alanine aminotransferase			
≥ 3× ULN	9/872 (1.0)	5/709 (0.7)	26/1551 (1.7)
≥ 5× ULN	1/872 (0.1)	1/709 (0.1)	2/1551 (0.1)
≥ 10× ULN	0	0	1/1551 (0.1)
Aspartate aminotransferase			
≥ 3× ULN	9/872 (1.0)	5/709 (0.7)	25/1551 (1.6)
≥ 5× ULN	5/872 (0.6)	2/709 (0.3)	11/1551 (0.7)
≥ 10× ULN	1/872 (0.1)	0	0

Data are *n*/NAR (%)

Fe iron, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *N* number of patients in the analysis set, *n* number of patients in the specified category, *NAR* number of patients at risk for the specified abnormality in each treatment group, *ULN* upper limit of normal

4 Discussion

There are multiple new therapies currently in development or already indicated for the treatment of patients with moderate-to-severe AD. Understanding the safety profile of these new medications is the key to an appropriate benefit-risk assessment by clinicians and patients. Dependent upon country-specific approvals, the recommended starting dose of baricitinib for adults with moderate-to-severe AD is 2 mg or 4 mg [20–22]. In this integrated analysis from eight clinical trials, we provide safety data for baricitinib 2 mg, including long-term data on over 1500 patients with a median follow-up of 330 days and maximum of 2.4 years. Baricitinib 2 mg demonstrated a safety profile in moderate-to-severe AD in this extended safety analysis consistent with the established safety profile for baricitinib 2 mg [19].

The most common TEAEs for baricitinib 2 mg were nasopharyngitis, headache, upper respiratory tract infection, nausea, diarrhea, and herpes simplex. The observed patterns and rates of common TEAEs were similar or numerically lower with prolonged exposure to baricitinib 2 mg.

Patients with moderate-to-severe AD have an increased susceptibility to cutaneous infection, including bacterial and herpes simplex infections, including EH [4, 5]. Baricitinib and other JAKi treatments have been associated with an increased risk of herpes simplex and HZ infections in RA [23–26]. Therefore, it was important to determine if baricitinib 2-mg treatment resulted in an increase in infections in patients with AD. Frequencies for HZ were low and slightly increased for baricitinib 2 mg vs placebo (0.8% vs 0.3%), with no increase in the IR of HZ with prolonged baricitinib 2-mg exposure. Herpes simplex (cluster) was reported more frequently with baricitinib 2 mg compared with placebo (3.8% vs 2.8%), and IRs were lower with extended exposure to baricitinib 2 mg (7.7 vs 13.2 during the first 16 weeks), suggesting that prolonged exposure to baricitinib 2 mg does not result in an increased rate of herpes simplex infections in patients with AD. A more significant trend for a decrease in the IR of infection with prolonged therapy was noted for skin infections requiring antibiotic treatment. Although similar IRs were observed between baricitinib 2 mg and placebo during the first 16 weeks (IR ~19.1), with prolonged treatment, the IR decreased to 2.6. This trend for a numeric decrease in herpes simplex and skin infections requiring antibiotics with prolonged therapy may suggest that an improvement in AD lesions may reduce the risk of these AEs with baricitinib 2 mg with long-term therapy. Frequencies of EH (cluster) were low with baricitinib 2 mg and placebo. To better characterize EH cases, data on the extent of herpetic lesions were collected, showing that the majority of EH cases involved small BSA (≤ 2% BSA), with 3/20 affecting 10% BSA or more according to investigators. Opportunistic infections were infrequent and similar between baricitinib 2 mg and placebo. Three opportunistic infections, all herpesvirus, were reported in All-bari-2-mg-AD.

Severe AD is associated with an increased risk of cardiovascular events [27–29]. In All-bari-2-mg AD, there were two events of positively adjudicated MACE (IR = 0.14), which is less than the background rates in the AD population for myocardial infarction (IR = 0.21), stroke (IR = 0.28), and cardiovascular death (IR = 0.44) [27], three individual outcomes commonly considered in the composite outcome of MACE. Thromboembolic events are a recognized adverse drug reaction with JAKis [30, 31]. There was one peripheral thrombosis and one arterial thrombosis in All-bari-2-mg-AD, but no PEs or DVTs in the analysis.

Conjunctival disorders are common in patients with AD [32]. Increased incidence in conjunctivitis has been reported in patients with AD receiving the anti-IL-4 receptor-α antibody, dupilumab, compared with placebo in clinical trials [33]. Based on the conjunctival disorder standardized MedDRA queries, the frequencies of conjunctival disorders were similar between baricitinib 2 mg and placebo and rates were numerically lower with prolonged exposure to baricitinib 2 mg, despite the expected inhibition of IL-4 and IL-13 by baricitinib, as both cytokines signal through JAKs [7].

There was a paucity of reported hematologic laboratory abnormalities (Grade 3 or 4) with baricitinib 2 mg compared with placebo, which did not confirm the expected JAK2 effects that can result in anemia, neutropenia, and thrombocytopenia [34]. Lipid increases (high-density lipoprotein and low-density lipoprotein) are consistent with a pharmacologic effect of JAK inhibition [34] and are a recognized drug reaction with baricitinib in RA [23]. Lipid increases were observed for low-density lipoprotein and high-density lipoprotein with baricitinib 2 mg compared with placebo, while triglycerides were largely unaffected. Importantly, these increases in lipids were not related to MACE or cardiovascular events. Increases in liver function tests (alanine aminotransferase, aspartate transaminase) have also been reported with JAKis [13, 23]. In this analysis, there were numerically fewer liver function test increases with baricitinib 2 mg than placebo. Increases in creatine phosphokinase have been observed with JAKis [13, 23]. The number of creatine phosphokinase increases to CTCAE Grade ≥ 3 were low and similar between baricitinib 2 mg and placebo, and most increases were asymptomatic.

In this integrated analysis, we observed no cases of DVT or PE, with few cases of MACE or malignancies, including NMSC, with baricitinib 2 mg. However, because malignancies and MACE can have a longer latency period, a longer treatment duration is required to better evaluate these risks. Atopic dermatitis is a chronic disease and additional long-term data will be essential to further understand other potential risks with extended baricitinib 2 mg exposure.

5 Conclusions

This integrated analysis in patients with moderate-to-severe AD confirms the established safety profile of baricitinib 2 mg.

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Ethics approval Trials were conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines and approved by the ethics committee or institutional review board of each center.

Consent to participate All patients provided written informed consent.

Consent for publication Not applicable.

Availability of data and material 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 USA and European Union 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, 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.

Code availability Not applicable.

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