




ORIGINAL ARTICLE

Pooled safety analysis of baricitinib in adult patients with atopic dermatitis from 8 randomized clinical trials

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Abstract

Background Janus kinase (JAK) inhibition is a new mode of action in atopic dermatitis (AD); clarity about drug class safety considerations in the context of AD is important. Baricitinib, an oral, reversible, selective inhibitor of JAK1/JAK2, is in late-stage development for adult patients with moderate-to-severe AD.

Objective To report pooled safety data for baricitinib in patients with moderate-to-severe AD in the clinical development program including long-term extension (LTE) studies.

Methods This analysis included patient-level safety data from six double-blinded, randomized, placebo-controlled studies (one phase 2 and five phase 3), one double-blinded, randomized, LTE study and one open-label LTE study, reported in three data sets: placebo-controlled, 2-mg – 4-mg extended and All-bari AD. Safety outcomes include treatment-emergent adverse events, adverse events of special interest and abnormal laboratory changes. Proportions of patients with events and incidence rates were calculated.

Results Data were collected for 2531 patients who were given baricitinib for 2247 patient-years (median duration 310 days). The frequency of serious infections, opportunistic infections and conjunctival disorders was low and similar between treatment groups in the placebo-controlled period. The most common serious infections were eczema herpeticum ($n = 11$, incidence rates (IR) = 0.5), cellulitis ($n = 6$, IR = 0.3) and pneumonia ($n = 3$, IR = 0.1). There were four opportunistic infections (IR = 0.2). No malignancies, gastrointestinal perforations, positively adjudicated cardiovascular events or tuberculosis were reported in the placebo-controlled period in baricitinib-treated patients. Frequency of herpes simplex was higher in the 4-mg group (6.1%) vs. the 2-mg (3.6%) and placebo group (2.7%); IRs in the extended data set (2-mg IR = 9.6; 4-mg IR = 14.5) were lower vs. the placebo-controlled data set (2-mg IR = 12.4; 4-mg IR = 21.3). In the All-bari AD data set, there were two positively adjudicated major adverse cardiovascular events (2-mg group): two venous thrombosis events (4-mg group) and one death.

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

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Conflicts of interest

Thomas Bieber reports personal fees from Eli Lilly and Company, during the conduct of the study; personal fees from pfizer, Bayer, AbbVie, Sanofi Genzyme, LEO, Galapagos, Glenmark, Galderma, Almirall, AnaptysBio, Arena Pharma, Asana, Boehringer Ingelheim, Dermavant, Incyte, Kymab, Menlo, Novartis and UCB outside the submitted work. Jacob P Thyssen reports personal fees from Pfizer, Eli Lilly and Company, AbbVie, LEO Pharma; grants and personal fees from

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Introduction

Atopic dermatitis (AD) is a highly pruritic inflammatory skin disease characterized by skin barrier dysfunction, excessive T-cell activation^{1–4} and increased susceptibility to cutaneous and systemic bacterial and viral infections.^{5–7} Signalling through the intracellular Janus kinases (JAKs; JAK1, JAK2 and tyrosine kinase 2) has been identified, as key cytokines are involved in the pathogenesis of AD.^{1,8,9}

Baricitinib, an oral, reversible, selective inhibitor of JAK1 and JAK2, is approved for the treatment of adult patients with moderately-to-severely active rheumatoid arthritis (RA) and is in late-stage development for adult patients with moderate-to-

severe AD and severe alopecia areata. To date, 13 148 patient-years exposure in clinical trials of RA are available.¹⁰ While JAK inhibition is well established in the treatment of RA, it is a new mode of action in dermatology and clarity about drug class safety considerations in the context of AD is important.

In completed phase 2 and 3 clinical trials, baricitinib as monotherapy and in combination with topical corticosteroids (TCS) improved signs and symptoms of AD.^{11–13} Here, we report pooled safety data of baricitinib in patients with moderate-to-severe AD from placebo-controlled phases of clinical trials and long-term extension (LTE) studies with exposure up to 2 years.

Clinicaltrials.gov: NCT02576938 (JAHG), NCT03334396 (JAHL; BREEZE-AD1), NCT03334422 (JAHM; BREEZE-AD2), NCT03334435 (JAHN; BREEZE-AD3), NCT03428100 (JAIN; BREEZE-AD4), NCT03435081 (JAIW; BREEZE-AD5), NCT03559270 (JAIX; BREEZE-AD6), NCT03733301 (JAII; BREEZE-AD7)

Methods

Study designs and patients

Safety data are included from six double-blinded, randomized clinical studies [phase 2: NCT02576938; phase 3: NCT03334396 (BREEZE-AD1), NCT03334422 (BREEZE-AD2), NCT03428100 (BREEZE-AD4), NCT03435081 (BREEZE-AD5), NCT03733301 (BREEZE-AD7)], one double-blinded, randomized, LTE [NCT03334435 (BREEZE-AD3)], and one open-label LTE [NCT03559270 (BREEZE-AD6)], with data cut-offs of 13 December 2019 (BREEZE-AD3) and 24 December 2019 (BREEZE-AD6) in the ongoing LTE studies. Study design and eligibility criteria are included in Table S1 (Supporting Information) and Appendix S1 (Supporting Information). Studies were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and approved by individual institutional review boards at each participating study centre. All patients provided written informed consent.

Analysis sets

Three integrated data sets were analysed:

- 1 Placebo-controlled data set: assessed the safety profile of 2-mg and 4-mg baricitinib vs. placebo during the 16-week, placebo-controlled period for patients in the phase 2 study and four phase 3 studies (BREEZE-AD1, BREEZE-AD2, BREEZE-AD4 and BREEZE-AD7). Some studies included 1-mg baricitinib which may be approved for renally impaired patients in some countries.
- 2 2-mg – 4-mg–extended data set (extended data set): evaluated the long-term safety profile from the randomized LTE study BREEZE-AD3 and the 16-week placebo-controlled data (including the phase 2 study and BREEZE-AD4). BREEZE-AD3 enrolled patients from originating studies BREEZE-AD1, BREEZE-AD2 and BREEZE-AD7 giving a total exposure up to 105 weeks of treatment.
- 3 All-bari AD data set (All-bari): provided estimates for incidence rates (IRs) of all adverse events (AEs) and assessment for less common event types, as it included data for all patients who received at least 1 dose (1-mg, 2-mg or 4-mg) of baricitinib from any of the 8 clinical trials at any time.

Safety outcomes

Treatment-emergent adverse events (TEAEs), including serious adverse events (SAEs), deaths and events leading to interruption or discontinuation of study drug; AEs of special interest; and abnormal laboratory changes, were evaluated (Table S2, Supporting Information). For some AEs of special interest, 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 (SMQs), medical assessment of PTs and clusters previously used to establish the safety profile of baricitinib in RA. Event clusters are described in Table S2 (Supporting Information).

Statistical analysis

Because the ratio of baricitinib to placebo randomization was not the same across all studies, adjusted percentages and adjusted IRs were calculated for AEs to provide appropriate direct comparisons between treatment groups for the placebo-controlled and extended data sets. Adjusted percentages were derived using study weights based on total sample size per study. Adjusted IRs per 100 patient-years at risk (PYR) of observation time, with observation time censored at event date, were derived using study weights based on total patient-years of exposure per study. For All-bari, IRs were calculated as the number of patients with an event per 100 PYR of observation time with observation time censored at event date.

Results

At baseline, disease characteristics and history of prior AD therapies were similar between baricitinib doses and placebo and across all data sets; approximately 47% of patients presented with severe AD (Table 1). For All-bari, 2531 patients (2247 PY) received ≥ 1 one dose of baricitinib and 42% of patients had ≥ 1 year exposure to baricitinib (Table 2); specifically, 14%, 29% and 51% of patients who received baricitinib 1-mg, 2-mg and 4-mg, respectively, had ≥ 1 year of exposure.

Treatment-emergent adverse events

In the placebo-controlled data set 43%, 49% and 51% of patients in the placebo, 2-mg and 4-mg groups, respectively, reported ≥ 1 TEAE (Table 2); the majority were mild or moderate in severity. Infections were the most common TEAEs, and the majority were mild or moderate in severity and were primarily upper respiratory tract infections and herpes simplex. In the placebo-controlled period, the frequency of infections was higher in baricitinib groups vs. placebo, but no dose-difference was noted. The IRs in the extended period were lower than during the placebo-controlled period (Table 2). The frequency of SAEs in the placebo, 2-mg and 4-mg groups were 2.3%, 1.4% and 2.3%, respectively; AD was the most commonly reported SAE PT. In the extended data set, TEAE IRs decreased in both baricitinib doses (Table 2). One death reported in All-bari after more than 12 months on baricitinib was due to gastrointestinal bleed in a patient randomized to 1-mg in originating study, then to 4-mg in LTE, and received a renally adjusted baricitinib dose (2-mg), due to a decreased glomerular filtration rate.

Study drug discontinuation (Table 3) and temporary interruptions are discussed in Appendix S2.

Adverse events of special interest

Infections The frequency of serious infections in the placebo-controlled data set was low and similar across treatment groups (Table 2). In the extended data set, IRs of serious infections were 1.5 and 3.0 for 2-mg and 4-mg, respectively. The most common serious infections in All-bari were eczema herpeticum ($n = 11$, IR = 0.5), cellulitis ($n = 6$, IR = 0.3) and pneumonia ($n = 3$, IR = 0.1). Similar proportions of patients in the placebo (4.4%) and 2-mg (4.8%) groups, and smaller proportion in the 4-mg (3.4%) group reported skin infections requiring antibiotic treatment. In the extended data set, the IR was lower in the 4-mg (4.3) vs. 2-mg group (7.5) and lower vs. the placebo-controlled period; IR was 3.4 in All-bari. In the skin infection cluster, the more common PTs in baricitinib-treated patients were folliculitis, cellulitis and impetigo.

There were no reports of tuberculosis. Opportunistic infections occurred infrequently with no differences between groups. In the placebo-controlled data set, 2 opportunistic infections were adjudicated: eye infection toxoplasmal (placebo) and multi-dermatomal herpes zoster (2-mg). In the All-bari data set, all adjudicated opportunistic infections were herpes zoster: two additional with multi-dermatomal herpes zoster (4-mg) and one patient with recurrent herpes zoster (2-mg).

More events of herpes zoster were reported in the 2-mg ($n = 6$, 0.8%) vs. placebo ($n = 3$, 0.3%) group; no events were reported in the 4-mg group. The number of herpes zoster events remained higher in the 2-mg ($n = 16$) vs. 4-mg ($n = 8$) group in the extended data set (Table 2). Across these data sets, no herpes zoster events were reported as SAEs or led to permanent discontinuations; only two events were reported as severe.

The proportion of patients reporting herpes simplex was higher in the 4-mg (6.1%) vs. placebo (2.7%) and 2-mg (3.6%) groups; the incidence in the extended data set was higher in the 4-mg (IR = 14.5) compared to 2-mg group (IR = 9.6), but was lower than in the placebo-controlled data set (Table 2). In All-bari herpes simplex IR was 10.3 ($n = 224$); 93% were mild or moderate in severity; the most common PTs were oral herpes ($n = 110$), herpes simplex ($n = 91$) and eczema herpeticum ($n = 32$; Table S3, Supporting Information). Of 43 patients who reported eczema herpeticum or Kaposi's varicelliform eruption, a majority (67.5%) had poor disease control prior to the event [Investigator Global Assessment for AD (IGA) scores of 3 or 4]. This relationship was not observed for initial episodes of oral herpes, where 52.7% of patients had IGA of 0, 1 or 2 before infection.

Cardiovascular events There were no reports of positively adjudicated MACE or other cardiovascular events during the placebo-controlled period. One myocardial infarction was adjudicated as MACE in the 2-mg group of the extended data set (IR = 0.17); risk factors included age, history of smoking,

hypertension, obesity, high cholesterol and pre-existing RA. In addition to this patient, one patient in All-bari (IR = 0.09) who had been randomized to placebo in the originating study and switched to 2-mg in the open-label LTE had a ruptured cerebral aneurysm that was positively adjudicated as haemorrhagic stroke. No gastrointestinal perforations were reported.

During the placebo-controlled period, there was one venous thromboembolic event (VTE), a pulmonary embolism (PE) in a 51-year-old female treated with 4-mg (IR = 0.38). Risk factors included concomitant use of oral contraceptives and being ex-smoker. The patient discontinued treatment and recovered from the event. In the extended data set, one additional event of PE occurred in the 4-mg group (IR = 0.40), a 61-year-old male with no clear risk factors other than age; baricitinib treatment was discontinued, and the patient was recovering. No deep vein thrombosis (DVTs) as defined by the external adjudication committee was reported. In the 2-mg group of the extended data set, there was one event adjudicated as peripheral venous thrombosis (below the knee DVT).

Malignancies There were no malignancies reported in either baricitinib group in the placebo-controlled or extended data sets. Two malignancies other than non-melanoma skin cancer (NMSC) occurred in the placebo group (IR = 0.66), one breast cancer and one papillary thyroid cancer. There was one NMSC (Bowen's disease) in a placebo patient (IR = 0.68). In All-bari, five malignancies other than NMSC were reported (IR = 0.22, Table 2), one patient each with anaplastic large cell lymphoma T- and null-cell types, B-cell lymphoma (symptoms began while on placebo), diffuse large B-cell lymphoma, prostate cancer and rectal cancer (all 2-mg except the patient with anaplastic large cell lymphoma who received 4-mg). In All-bari, six NMSC were reported (IR = 0.26): basal cell carcinoma ($n = 3$, all 2-mg), Bowen's disease ($n = 2$, 4-mg) and keratoacanthoma ($n = 1$, 4-mg).

Conjunctival disorders Within the SMQ cluster of conjunctival disorders, in the placebo-controlled data set, 1.6% and 1.2% of patients in the 2-mg and 4-mg groups, respectively, reported events compared to 2.1% in the placebo group. In the extended data set, IRs were similar between doses (2-mg = 4.9; 4-mg = 4.6) and similar to All-bari (4.3). PTs most commonly reported were conjunctivitis (41% of conjunctival disorders in All-bari) and allergic conjunctivitis (35%) (Table S3, Supporting Information).

Laboratory evaluation Increase in serum creatine phosphokinase (CPK) to at least Grade 1 [$>$ upper level normal (ULN) to $2.5 \times$ ULN] was the most common laboratory change and was recorded for 19.3% and 23.8% of patients in the 2-mg and 4-mg groups, respectively, vs. 10.3% in the placebo group; frequencies were also higher for baricitinib groups vs. placebo for CPK

Table 1 Baseline demographics and measures of disease activity

	Placebo-controlled (to week 16)			All-bari-AD
	Placebo (N = 743)	Bari 2-mg (N = 576)	Bari 4-mg (N = 489)	All-bari-AD (N = 2531)†
Age at baseline, years	35.7 (13.1)	35.9 (13.5)	35.8 (13.2)	36.4 (13.7)
Female, n (%)	298 (40.1)	205 (35.6)	170 (34.8)	994 (39.3)
Body mass index, kg/m ²	25.4 (5.2)	25.8 (5.5)	25.5 (5.1)	25.9 (5.4)
Duration since AD diagnosis, years	24.9 (14.6)	25.0 (14.3)	24.7 (14.8)	25.0 (14.9)
Geographic region, n (%)				
Central/South America and Mexico	76 (10.2)	56 (9.7)	42 (8.6)	257 (10.2)
USA/Canada (including Puerto Rico)	41 (5.5)	31 (5.4)	32 (6.5)	468 (18.5)
Asia (excluding Japan)	99 (13.3)	62 (10.8)	66 (13.5)	235 (9.3)
Japan	134 (18.0)	101 (17.5)	89 (18.2)	341 (13.5)
Europe	365 (49.1)	297 (51.6)	237 (48.5)	1109 (43.8)
Rest of the world	28 (3.8)	29 (5.0)	23 (4.7)	121 (4.8)
Prior topical therapy, n (%)				
Topical corticosteroids	646 (86.9)	496 (86.1)	430 (87.9)	2255 (89.1)
Topical calcineurin inhibitor	410 (61.6)	316 (65.8)	275 (65.2)	1291 (55.4)
Prior systemic therapy				
Cyclosporine	254 (38.7)	255 (52.8)	172 (41.1)	791 (34.0)
Disease characteristics				
vIGA-AD score of 4 (severe disease), n (%)	324 (46.7)	257 (47.7)	211 (46.8)	1037 (46.9)
EASI score	31.5 (12.7)	31.3 (13.2)	32.1 (12.9)	31.1 (12.8)
SCORAD	67.8 (13.3)	67.9 (13.4)	68.1 (13.2)	67.5 (13.4)
Per cent body surface area affected	51.2 (22.6)	51.2 (23.0)	52.9 (22.5)	50.3 (23.2)
DLQI	14.5 (7.7)	14.0 (7.6)	14.0 (7.9)	14.2 (7.7)
Itch NRS	6.9 (2.0)	6.6 (2.2)	6.7 (2.1)	6.8 (2.1)

Data reported as mean (SD) unless otherwise indicated.

AD, atopic dermatitis; Bari, baricitinib; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; n, number of patients in the specified category; N, number of patients; NRS, numeric rating scale; SCORAD, SCORing Atopic Dermatitis; vIGA-ADtm, validated Investigator Global Assessment for Atopic Dermatitis.

†All-bari AD includes bari 1-mg, 2-mg and 4-mg doses.

increases to at least Grades 2 and 3 (Table 4). There were no haemoglobin Grade 3 (<8 mg/dL) or higher changes with either baricitinib dose in any data set. Few patients had lymphocyte counts <500 cells/mm³ or neutrophil counts <1000 cells/mm³. Decreases of neutrophils to <1000 cells/mm³ were not associated with serious infections and did not lead to study drug discontinuation. Increases in platelets to >600 × 10⁹/L occurred in a higher proportion of patients in the 2-mg (1.2%) and 4-mg (0.6%) groups vs. placebo (0%); proportions were similar in the extended data set. No AEs at the time of the maximum platelet count were related to increased platelets. A higher proportion of patients in the baricitinib groups vs. placebo had categorical increases in LDL and HDL (Table 4); given the low occurrence of MACE or cardiovascular events, these data do not indicate an increased risk. Across all data sets, few patients experienced ≥3× or ≥5× ULN for alanine aminotransferase (ALT) and only one patient in All-bari experienced ≥10× ULN ALT. There was no evidence that treatment with baricitinib was associated with an increased risk of hepatic-related TEAEs or SAEs leading to temporary interruption or permanent discontinuation of study

drug. More detailed information on laboratory evaluations can be found in Appendix S2 and Fig. S1.

Discussion

We report integrated safety data from the baricitinib AD clinical program. The safety profile of baricitinib in the treatment of RA has been well established.^{14–17} Compared to patients with RA, patients with AD are younger (more of childbearing potential), more equal in gender, and have different concomitant medications and associated comorbidities. Therefore, it is important to establish baricitinib's safety profile in AD.

During the placebo-controlled period, the proportion of patients reporting TEAEs was similar between baricitinib 2-mg and 4-mg; both doses were higher than placebo. Frequencies for SAEs were low (<2.5%) in this AD population and IRs for baricitinib doses were similar to placebo. The most common TEAEs in the baricitinib groups were nasopharyngitis, headache, CPK elevations and diarrhoea. Headaches were mostly mild and short in duration (median <1 day). Dose-dependent elevations in

Table 2 Overview of safety measures including drug exposure, treatment-emergent adverse events and adverse events of special interest

	Placebo-controlled (to week 16)			2-mg – 4-mg extended		All-bari- AD†
	Placebo (N = 743)	Bari 2-mg (N = 576)	Bari 4-mg (N = 489)	Bari 2- mg† (N = 576)	Bari 4-mg (N = 489)	All-Bari-AD (N = 2531)†
Exposure						
Total patient-years	211.8	169.1	147.1	425.5	459.3	2247.4
No. of patients with ≥52 weeks, n (%)	—	—	—	175 (30.4)	208 (42.5)	1060 (41.9)
Median duration, days	113.0	113.0	113.0	261.5	311.0	310.0
Longest exposure, days	168	128	155	736	731	736
Adverse events, n (adj %) [adj IR]§						
Any TEAE	388 (43.2) [234.7]	347 (49.3) [281.4]	300 (51.0) [300.1]	402 [237.3]	377 [248.3]	1765 [186.1]
SAE	21 (2.3) [8.0]	10 (1.4) [4.4]	14 (2.3) [7.7]	17 [3.5]	40 [9.1]	138 [6.1]
Interruption of study drug due to AE	14 (1.6) [5.4]	27 (3.4) [11.6]	26 (4.6) [15.8]	47 [10.4]	54 [12.7]	218 [9.9]
Discontinuation of study drug due to AE	13 (1.4) [4.6]	10 (1.5) [4.7]	15 (2.1) [6.5]	18 [3.6]	27 [5.5]	105 [4.6]
Death, n (IR)	0	0	0	0	0	1 (0.0)
Infections, n (adj %) [adj IR]§						
Treatment-emergent infections	216 (24.2) [100.3]	212 (29.8) [128.0]	183 (31.5) [134.5]	294 [115.4]	281 [117.4]	1272 [91.7]
Serious infection	5 (0.6) [2.1]	3 (0.4) [1.0]	3 (0.6) [1.9]	8 [1.5]	13 [3.0]	48 [2.1]
Herpes zoster	3 (0.3) [1.0]	6 (0.8) [2.7]	0	16 [3.8]	8 [1.8]	53 [2.3]
Herpes simplex¶	22 (2.7) [9.4]	25 (3.6) [12.4]	35 (6.1) [21.3]	41 [9.6]	59 [14.5]	224 [10.3]
Eczema herpeticum††	4 (0.4) [1.3]	1 (0.2) [0.7]	7 (1.4) [4.5]	5 [1.1]	12 [2.6]	43 [1.9]
Skin infections requiring antibiotic treatment	38 (4.4) [15.7]	31 (4.8) [16.7]	18 (3.4) [11.4]	31 [7.5]	18 [4.3]	75 [3.4]
Tuberculosis	0	0	0	0	0	0
Opportunistic infection excluding TB	1 (0.1) [0.4]	1 (0.1) [0.3]	0	1 [0.2]	1 [0.3]	4 [0.2]
Malignancy, n (adj %) [adj IR]§						
Malignancy excl NMSC	2 (0.2) [0.66]	0	0	0	0	5 [0.22]
NMSC	1 (0.2) [0.68]	0	0	0	0	6 [0.26]
Adverse cardiovascular events of special interest, n (adj %) [adj IR]†						
MACE	0	0	0	1 [0.17]	0	2 [0.09]
VTE (DVT and/or PE)	0	0	1 (0.1) [0.38]	0	2 [0.40]	2 [0.09]
DVT	0	0	0	0	0	0
PE	0	0	1 (0.1) [0.38]	0	2 [0.40]	2 [0.09]
GI disorder, n (adj %) [adj IR]§						
GI perforations	0	0	0	0	0	0
Ocular AEs, n (adj %) [adj IR]§						
Conjunctival disorders	15 (2.1) [7.5]	12 (1.6) [5.6]	6 (1.2) [3.7]	21 [4.9]	18 [4.6]	96 [4.3]

AD, atopic dermatitis; AE, adverse events; Bari, baricitinib; CV, cardiovascular; DVT, deep vein thrombosis; EAIR, exposure-adjusted incidence rate; GI, gastrointestinal; IR, incidence rate; MACE, major adverse cardiovascular events; HZ herpes zoster; LTE, long-term extension; MI, myocardial infarction; PE, pulmonary embolism; n, number of patients in the specified category; N, number of patients in the analysis set; NMSC, nonmelanoma skin cancer; PY, patient-years; RA, rheumatoid arthritis; SAE, serious adverse event; TB, tuberculosis; TEAE, treatment-emergent adverse events; VTE, venous thromboembolism.

†All-bari AD includes bari 1-mg, 2-mg, and 4-mg. ‡Ninety-nine patients on 2-mg baricitinib in the originating studies who were non-responders were re-randomized to 4-mg at entry to BREEZE-AD3; their data were censored at start of the 4-mg dose in the LTE. §IRs for the placebo-controlled datasets and the 2-mg – 4-mg dataset are study-size adjusted rates; adjusted percentages are only shown for the placebo-controlled dataset. ¶Herpes simplex included PTs of herpes simplex, oral herpes, Kaposi's varicelliform eruption, eczema herpeticum, ophthalmic herpes simplex, genital herpes, and genital herpes simplex.

††This row of data comes from the cluster that contains the preferred terms eczema herpeticum and Kaposi's varicelliform eruption.

CPK were mostly asymptomatic and not associated with muscle-related symptoms and no cases of rhabdomyolysis. The most notable feature in the majority of patients with CPK >5× ULN was the presence of recent strenuous exercise. These patterns and rates of common TEAEs were similar or lower with prolonged treatment to both doses.

Patients with AD have an increased risk of bacterial and viral infections, both cutaneous and non-cutaneous, due to defective skin barrier and immunologic dysregulation.⁶ Eczema herpeticum is an acute, disseminated skin infection, most commonly caused by herpes simplex virus, and represents a typical complication of AD occurring in approximately 3% of patients.⁵

Table 3 Adverse events detail

	Placebo-controlled (to week 16)			2-mg-4-mg-extended		All-Bari-AD (N = 2531) [PY = 2247]
	Placebo (N = 743) [PY = 212]	Bari 2-mg (N = 576) [PY = 169]	Bari 4-mg (N = 489) [PY = 147]	Bari 2-mg (N = 576) [PY = 426]	Bari 4-mg (N = 489) [PY = 459]	
	TEAE occurring in ≥2% of patients in any group in the placebo-controlled data sets, n (adj %) [adj IR]					
Nasopharyngitis	83 (9.5) [34.9]	67 (9.5) [34.1]	67 (11.3) [40.8]	106 [28.6]	117 [34.1]	439 [22.0]
Headache	28 (3.3) [11.9]	37 (5.9) [21.1]	35 (6.3) [21.4]	43 [10.8]	46 [10.6]	166 [7.6]
Blood creatine phosphokinase increased	6 (0.8) [2.7]	8 (1.1) [3.5]	17 (2.9) [9.6]	9 [2.0]	24 [5.0]	63 [2.8]
Diarrhoea	15 (1.8) [6.2]	10 (1.3) [4.3]	15 (2.7) [9.0]	15 [3.1]	19 [4.6]	78 [3.5]
Herpes simplex	8 (0.9) [3.2]	13 (2.0) [7.1]	15 (2.6) [8.6]	19 [4.5]	28 [6.2]	91 [4.0]
Upper respiratory tract infection	14 (1.4) [4.8]	23 (3.2) [11.0]	15 (2.5) [8.3]	31 [7.7]	36 [7.7]	160 [7.2]
Upper abdominal pain	10 (1.2) [4.1]	10 (1.6) [5.3]	14 (2.5) [8.5]	14 [3.2]	15 [3.6]	42 [1.8]
Influenza	8 (1.0) [3.4]	13 (1.7) [5.7]	12 (2.2) [7.2]	23 [5.0]	25 [7.1]	100 [4.4]
Oral herpes	9 (1.2) [4.1]	10 (1.2) [4.2]	12 (2.0) [6.7]	17 [4.0]	28 [6.6]	110 [4.9]
Urinary tract infection	8 (0.8) [2.6]	9 (1.1) [3.8]	11 (2.0) [6.5]	15 [3.4]	14 [3.4]	72 [3.2]
Folliculitis	11 (1.2) [4.0]	14 (1.8) [6.2]	10 (1.5) [4.9]	19 [4.1]	14 [2.8]	72 [3.2]
Nausea	8 (0.8) [2.7]	14 (1.8) [5.8]	4 (0.8) [2.5]	16 [3.4]	8 [1.8]	49 [2.1]
Permanent discontinuation of study drug due to adverse event by system organ class, n (adj %) [adj IR]						
Skin and subcutaneous tissue disorders†	3 (0.3) [0.9]	2 (0.2) [0.7]	5 (0.7) [2.1]	3 [0.6]	9 [1.7]	27 [1.2]
Infections and infestations	2 (0.2) [0.7]	2 (0.3) [1.0]	2 (0.4) [1.3]	5 [0.9]	6 [1.5]	20 [0.9]
Investigations	1 (0.2) [0.7]	1 (0.2) [0.7]	3 (0.4) [1.0]	1 [0.3]	6 [1.1]	15 [0.6]
Respiratory, thoracic and mediastinal disorders	0	0	2 (0.2) [0.8]	0	1 [0.2]	3 [0.1]
Gastrointestinal disorders	0	1 (0.1) [0.3]	1 (0.1) [0.4]	2 [0.3]	1 [0.2]	8 [0.3]
Nervous system disorders	2 (0.2) [0.7]	0	1 (0.1) [0.3]	0	1 [0.2]	5 [0.2]
Renal and urinary disorders	0	0	1 (0.6)	0	1 [0.2]	1 [0.0]
Blood and lymphatic system disorders	3 (0.3) [0.9]	1 (0.1) [0.4]	0	1 [0.2]	0	2 [0.1]
Eye disorders	0	1 (0.2) [0.7]	0	1 [0.3]	0	2 [0.1]
General disorders and administrative site conditions	0	1 (0.1) [0.3]	0	2 [0.3]	0	4 [0.2]
Psychiatric disorders	0	1 (0.2) [0.7]	0	1 [0.3]	0	2 [0.1]
Congenital, familial and genetic disorders	0	0	0	0	0	2 [0.1]

†The preferred terms under the SOC 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.

Interferons (IFNs) are the first line of host defence against viral infections. Especially in AD patients with a history of eczema herpeticum, there is an increased risk of recurrent and disseminated viral infections, including herpes simplex and herpes zoster, related to the insufficient production of IFNs with down regulation of the receptor.^{18,19} Therefore, it is important to assess whether treatment with baricitinib resulted in an increase in herpes infections.

In this analysis, reports of herpes zoster were low, did not show dose-dependent increases (no cases in the 4-mg group during placebo-controlled period) and were lower than reported in RA.¹⁴ Herpes simplex, however, was reported more frequently in the AD program compared to the RA program¹⁴ and was reported more frequently for baricitinib 4-mg vs. 2-mg in the placebo-controlled data set. However, the IR for herpes simplex for both doses decreased in the extended data set and was lower in All-bari than either dose during the placebo-controlled period. This suggests prolonged treatment with baricitinib did not result in a continuous increase in the incidence of herpes

infections. Eczema herpeticum infections appear to be correlated with extent of AD disease severity in the baricitinib AD data set and may indicate that initial increases in eczema herpeticum eruptions with baricitinib 4-mg are offset with prolonged therapy by improvements in AD lesions. There was no increase in eczema herpeticum cases with the 2-mg dose. Data from both baricitinib and dupilumab clinical development programs suggest better control of skin disease reduces the frequency of eczema herpeticum.²⁰

There were no increases in skin infections or skin infections requiring antibiotic treatment in the studies in the extended data sets. Staphylococcus aureus colonization is strongly linked to more severe barrier dysfunction, skin infections and exacerbation of AD. The density of Staphylococcus aureus on the skin of patients with AD has also been shown to be associated with higher disease severity.²¹ Staphylococcus aureus infections include impetigo, cellulitis, abscesses and invasive infections. Almost 50% of patients in the current analysis presented with severe AD at baseline. In line with this, AD was the most

Table 4 Changes in selected laboratory values and clinical chemistry

Treatment-emergent changes, n/NAR (%)	Placebo-controlled (to week 16)			2-mg-4-mg extended [†]		All-Bari-AD (N = 2531)
	Placebo (N = 743)	Bari 2-mg (N = 576)	Bari 4-mg (N = 489)	Bari 2-mg (N = 576)	Bari 4-mg (N = 489)	
LDL \geq130 mg/dL	34/542 (6.3)	52/435 (12.0)	48/363 (13.2)	85/437 (19.5)	93/366 (25.4)	408/1868 (21.8)
HDL \geq60 mg/dL	65/442 (14.7)	70/360 (19.4)	75/297 (25.3)	91/362 (25.1)	102/300 (34.0)	443/1500 (29.5)
Triglycerides \geq500 mg/dL	5/662 (0.8)	3/510 (0.6)	3/437 (0.7)	6/514 (1.2)	5/440 (1.1)	22/2269 (1.0)
Creatine phosphokinase (U/L)						
>ULN–2.5 \times ULN	69/667 (10.3)	99/513 (19.3)	106/446 (23.8)	134/513 (26.1)	160/446 (35.9)	634/2201 (28.8)
>2.5 \times ULN–5 \times ULN	22/717 (3.1)	27/559 (4.8)	31/477 (6.5)	39/559 (7.0)	49/477 (10.3)	196/2430 (8.1)
>5 \times ULN–10 \times ULN	14/723 (1.9)	14/564 (2.5)	16/487 (3.3)	19/564 (3.4)	24/487 (4.9)	95/2471 (3.8)
\geq 10 \times ULN	9/727 (1.2)	7/567 (1.2)	7/488 (1.4)	10/567 (1.8)	12/488 (2.5)	51/2483 (2.1)
Haemoglobin						
<LLN	31/688 (4.5)	31/538 (5.8)	44/456 (9.6)	48/538 (8.9)	64/456 (14.0)	221/2320 (9.5)
<10 mg/dL	2/728 (0.3)	1/569 (0.2)	4/486 (0.8)	4/569 (0.7)	5/486 (1.0)	22/2492 (0.9)
<8 mg/dL	0	0	0	0	0	0
Neutrophils <1000 cells/mm³	0	1/570 (0.2)	1/487 (0.2)	1/570 (0.2)	3/487 (0.6)	6/2491 (0.2)
Lymphocytes <500 cells/mm³	1/726 (0.1)	0	3/487 (0.6)	0	4/487 (0.8)	12/2492 (0.5)
Platelets						
>600 billions/L	0	7/568 (1.2)	3/482 (0.6)	11/568 (1.9)	4/482 (0.8)	26/2485 (1.0)
Patients with any postbaseline elevation, n/N (%) ALT						
\geq 3 \times ULN	7/725 (1.0)	3/569 (0.5)	1/488 (0.2)	5/569 (0.9)	8/488 (1.6)	40/2480 (1.6)
\geq 5 \times ULN	1/729 (0.1)	1/569 (0.2)	1/488 (0.2)	1/569 (0.2)	1/488 (0.2)	5/2494 (0.2)
\geq 10 \times ULN	0	0	0	0	0	1/2498 (0.0)

ALT, Alanine Aminotransferase; Bari, baricitinib; LLN, lower level of normal; N, number of patients in the safety analysis set; n, number of patients in the specified category; NAR, number of patients at risk for the specified abnormality; ULN, upper level of normal.

[†]Data up to dose change for the 2-mg – 4-mg extended dataset

common SAE PT, reported in half of patients in All-bari who discontinued study drug due to TEAEs. Of note, for skin infections requiring antibiotic treatment, incidences were lower in the 4-mg vs. 2-mg and placebo groups, which could likely be attributable to the positive effect on improving skin integrity in patients with AD.

No increase in MACE was noted. Severe and predominantly active AD are independently associated with increased risk of cardiovascular events (approximately 20–70% increased risk compared to general population).^{22,23} In patients with AD, reported IRs of three individual outcomes commonly considered in the composite outcome of MACE range from 0.2 and 0.27 for myocardial infarction and stroke, respectively, to 0.44 for cardiovascular death.^{22,24} In All-bari AD, there were two reports of positively adjudicated MACE (IR: 0.09), which is less than the background rate for these events.^{22,24} It is unknown whether patients with AD are at an increased risk of VTE; however, thromboembolic events are a recognized adverse drug reaction of JAK inhibitors^{25,26} and warranted examination in this analysis. The observed incidence of VTE in the All-bari AD data set is limited to two cases of PE; while this observed IR (0.09) cannot be precise, it is similar to the IR in the overall population (~1 per 1000 in adult populations).^{27,28} With consideration of the

limitations of this comparison, the present data do not indicate a clear risk for VTE in the AD population and the risk with baricitinib remains in a similarly low range.

Conjunctival disorders, specifically allergic conjunctivitis, are common in patients with AD. Based on the conjunctival disorders MedDRA SMQ, the proportion of patients with a conjunctival disorder was lower in the baricitinib vs. placebo groups. In contrast, a report of conjunctivitis in AD trials of dupilumab showed a higher proportion of patients treated with dupilumab (8.6–22.1%) had conjunctivitis (based on select PTs that included conjunctivitis, allergic conjunctivitis, bacterial conjunctivitis, viral conjunctivitis, adenoviral conjunctivitis and atopic keratoconjunctivitis) compared to placebo-treated patients (2.1–11.1%).²⁹ In the current analysis, the IR for the cluster of conjunctival disorders in All-bari was 4.3, whereas infectious conjunctivitis (MedDRA PT) in dupilumab was reported at an IR of 9.705 for both doses compared to 1.975 for placebo.²¹ Despite the fact that dupilumab's targets (IL-13 and IL-4) both signal through JAKs and are expected to be modulated by baricitinib, conjunctivitis was not seen as an issue in this analysis, suggesting baricitinib may represent a reasonable treatment option for patients who experience eye symptoms with dupilumab.

Minimal changes in haemoglobin, neutrophil, lymphocyte and platelet counts were observed. This paucity of changes in haematologic parameters is in contrast to recently disclosed data from abrocitinib where dose-dependent decreases in platelets were reported in AD patients.^{30,31} Lipid increases were noted in both LDL and HDL, but more commonly in HDL. Baricitinib treatment is associated with small, reversible and dose-dependent increases in serum creatinine. The observed changes in serum creatinine are thought to be due to competitive inhibition of creatinine secretion by baricitinib in the renal tubules leading to slightly reduced estimates of the glomerular filtration rate without actual loss of renal function or the occurrence of renal AEs. In the current study, minor dose-dependent increases in serum creatinine were observed with baricitinib; however, there was no evidence baricitinib treatment was associated with increased risk of serious renal AEs, such as renal failure, impairment or injury. These results are similar to previous findings for baricitinib in patients with diabetic kidney disease and low glomerular filtration rate (25–70 mL/min/1.73 m²) showing no renal safety signals observed in a phase 2 study.³²

Limitations of study

The IRs provide an estimate of the number of patients experiencing an event per 100 patient-years of exposure and can be viewed in context with IRs from the literature. However, any comparisons are for context only; inferences cannot be made as study and treatment are confounded and risk over time can change due to reasons other than treatment exposure. Other limitations are similar to observational data. Regarding malignancies and MACE, longer treatment duration is required to better evaluate risks.

Conclusion

This integrated safety analysis in patients with moderate-to-severe AD, confirms the established safety profile of baricitinib and indicates some quantitative differences in TEAEs might be attributable to the disease characteristics.

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Data Sharing statement

Eli Lilly and Company 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 United States and the 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 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.

References

- Brunner PM, Guttman-Yassky E, Leung DY. The immunology of atopic dermatitis and its reversibility with broad-spectrum and targeted therapies. *J Allergy Clin Immunol* 2017; **139**: S65–S76.
- Czarnowicki T, He H, Krueger JG, Guttman-Yassky E. Atopic dermatitis endotypes and implications for targeted therapeutics. *J Allergy Clin Immunol* 2019; **143**: 1–11.
- Werfel T, Allam JP, Biedermann T et al. Cellular and molecular immunologic mechanisms in patients with atopic dermatitis. *J Allergy Clin Immunol* 2016; **138**: 336–349.
- Brunner PM, Silverberg JI, Guttman-Yassky E et al. Increasing comorbidities suggest that atopic dermatitis is a systemic disorder. *J Invest Dermatol* 2017; **137**: 18–25.
- Ong PY, Leung DY. Bacterial and viral infections in atopic dermatitis: a comprehensive review. *Clin Rev Allergy Immunol* 2016; **51**: 329–337.
- Langan SM, Abuabara K, Henrickson SE, Hoffstad O, Margolis D. Increased risk of cutaneous and systemic infections in atopic dermatitis – a cohort study. *J Invest Dermatol* 2017; **137**: 1375–1377.
- Narla S, Silverberg JI. Association between atopic dermatitis and serious cutaneous, multiorgan and systemic infections in US adults. *Ann Allergy Asthma Immunol* 2018; **120**: 66–72.
- Schwartz DM, Bonelli M, O'Shea GM. Type I/II cytokines, JAKs, and new strategies for treating autoimmune diseases. *Nat Rev Rheumatol* 2016; **12**: 25–36.
- Esaki H, Ewald DA, Ungar B et al. Identification of novel immune and barrier genes in atopic dermatitis by means of laser capture microdissection. *J Allergy Clin Immunol* 2015; **135**: 153–163.
- Genovese MC, Smolen JS, Takeuchi T et al. Safety profile of baricitinib for the treatment of rheumatoid arthritis up to 8.4 years: an updated integrated safety analysis. *Ann Rheum Dis* 2020; **79**(Suppl 1): 638–639.
- Guttman-Yassky E, Silverberg JI, Nemoto O et al. Baricitinib in adult patients with moderate-to-severe atopic dermatitis: A phase 2 parallel, double-blinded, randomized placebo-controlled multiple-dose study. *J Am Acad Dermatol* 2018; **80**: 913–921.
- Simpson EL, Lacour J-P, Spelman L et al. Baricitinib in patients with moderate-to-severe atopic dermatitis and inadequate response to topical corticosteroids: results from two randomized monotherapy phase III trials. *Br J Dermatol* 2020; **183**: 242–255. <https://doi.org/10.1111/bjd.18898>.
- Reich K, Kabashima K, Peris K et al. Efficacy and safety of baricitinib in combination with topical corticosteroids in moderate to severe atopic dermatitis: results of a phase 3 randomized, double-blind, placebo-controlled 16-week trial (BREEZE-AD7). European Academy of Dermatology and Venereology - 28th Congress; 2019.
- Genovese MC, Smolen JS, Takeuchi T et al. Safety profile of baricitinib for the treatment of rheumatoid arthritis over a median of 3 years treatment: an updated integrated safety analysis. *Lancet Rheumatol* 2020; **2**: E347–E357.
- Smolen JS, Genovese MC, Takeuchi T et al. Safety profile of baricitinib in patients with active rheumatoid arthritis with over 2 years median time in treatment: an integrated analysis. *J Rheumatol* 2019; **46**: 7–18.

- 16 Taylor PC, Weinblatt ME, Burmester GR *et al.* Cardiovascular safety during treatment with baricitinib in rheumatoid arthritis. *Arthritis Rheumatol* 2019; **71**: 1042–1055.
- 17 Winthrop KL, Harigai M, Genovese MC *et al.* Infections in the baricitinib clinical development Program for patients with active rheumatoid arthritis. *Ann Rheum Dis* 2020; **79**: 1290–1297.
- 18 Kwon HJ, Bang DW, Kim EN *et al.* Asthma as a risk factor for zoster in adults: a population-based case-control study. *J Allergy Clin Immunol* 2016; **137**: 1406–1412.
- 19 Traidl S, Kienlin P, Begemann G *et al.* Patients with atopic dermatitis and history of eczema herpeticum elicit herpes simplex virus-specific type 2 immune responses. *J Allergy Clin Immunol* 2018; **141**: 1144–1147.e5.
- 20 Eichenfield LF, Bieber T, Beck LA *et al.* Infections in dupilumab clinical trials in atopic dermatitis: a comprehensive pooled analysis. *Am J Clin Dermatol* 2019; **20**: 443–456.
- 21 Tauber M, Balica S, Hsu C-Y *et al.* *Staphylococcus aureus* density on lesional and nonlesional skin is strongly associated with disease severity in atopic dermatitis. *J Allergy Clin Immunol* 2016; **137**: 1272–1274.
- 22 Silverwood RJ, Forbes HJ, Abuabara K *et al.* Severe and predominantly active atopic eczema in adulthood and long term risk of cardiovascular disease: population based cohort study. *BMJ* 2018; **361**: k1786.
- 23 Yuan M, Cao WF, Xie XF, Zhou HY, Wu XM. Relationship of atopic dermatitis with stroke and myocardial infarction: a meta-analysis. *Medicine (Baltimore)* 2018; **97**: e13512.
- 24 Andersen YMF, Egeberg A, Gislason GH, Hansen PR, Skov L, Thyssen JP. Risk of myocardial infarction, ischemic stroke, and cardiovascular death in patients with atopic dermatitis. *J Allergy Clin Immunol* 2016; **138**: 310–312.e3.
- 25 Scott IC, Hider SL, Scott DL. Thromboembolism with Janus kinase (JAK) inhibitors for rheumatoid arthritis: how real is the risk? *Drug Saf* 2018; **41**: 645–653.
- 26 Verden A, Dimbil M, Kyle R, Overstreet B, Hoffman K. Analysis of spontaneous postmarket case reports submitted to the FDA regarding thromboembolic adverse events and JAK inhibitors. *Drug Saf* 2018; **41**: 357–361.
- 27 Cushman M. Epidemiology and risk factors for venous thrombosis. *Semin Hematol* 2007; **44**: 62–69.
- 28 Heit JA. Epidemiology of venous thromboembolism. *Nat Rev Cardiol* 2015; **12**: 464–474.
- 29 Akinlade B, Guttman-Yassky E, de Bruin-Weller M *et al.* Conjunctivitis in dupilumab clinical trials. *Br J Dermatol* 2019; **181**: 436–437.
- 30 Silverberg JL, Simpson EL, Thyssen JP *et al.* Efficacy and safety of abrocitinib in patients with moderate-to-severe atopic dermatitis a randomized clinical trial. *JAMA Dermatol* 2020; **156**: 863.
- 31 Gooderham MJ, Forman SB, Bissonnette R *et al.* Efficacy and safety of oral Janus kinase 1 inhibitor abrocitinib for patients with atopic dermatitis a phase 2 randomized clinical trial. *JAMA Dermatol* 2019; **155**: 1371–1379.
- 32 Tuttle KR, Brosius DC, 3rd, Adler S *et al.* JAK1/JAK2 inhibition by baricitinib in diabetic kidney disease: results from a phase 2 randomized controlled clinical trial. *Nephrol Dial Transplant* 2018; **33**: 1950–1959.

Supporting information

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

Fig. S1. Change from baseline in selected laboratory evaluations.

Table S1. Baricitinib trials included in the integrated analysis.

Table S2. Safety outcomes definitions.

Table S3. Herpes simplex and conjunctivitis preferred terms used.

Appendix S1. Key inclusion and exclusion criteria in the baricitinib atopic dermatitis clinical program.

Appendix S2. Study drug discontinuation and temporary interruption.

Appendix S3. Laboratory evaluations.