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Angaben zur Veröffentlichung / Publication details:

Wollenberg, Andreas, Masanori Ikeda, Chia-Yu Chu, Lawrence F. Eichenfield, Marieke M. B. Seyger, Apurva Prakash, Robinette Angle, Danting Zhu, Marco Pontes, and Amy S. Paller. 2024. "Longer-term safety and efficacy of baricitinib for atopic dermatitis in pediatric patients 2 to <18 years old: a randomized clinical trial of extended treatment to 3.6 years." Journal of Dermatological Treatment 35 (1): 2411834. https://doi.org/10.1080/09546634.2024.2411834.

Journal of Dermatological Treatment

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ijdt20

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To cite this article: Andreas Wollenberg, Masanori Ikeda, Chia-Yu Chu, Lawrence F. Eichenfield, Marieke M. B. Seyger, Apurva Prakash, Robinette Angle, Danting Zhu, Marco Pontes & Amy S. Paller (2024) Longer-term safety and efficacy of baricitinib for atopic dermatitis in pediatric patients 2 to <18 years old: a randomized clinical trial of extended treatment to 3.6 years, Journal of Dermatological Treatment, 35:1, 2411834, DOI: 10.1080/09546634.2024.2411834

To link to this article: https://doi.org/10.1080/09546634.2024.2411834

JOURNAL OF DERMATOLOGICAL TREATMENT
2024, VOL. 35, NO. 1, 2411834
https://doi.org/10.1080/09546634.2024.2411834

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RESEARCH ARTICLE

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Longer-term safety and efficacy of baricitinib for atopic dermatitis in pediatric patients 2 to <18 years old: a randomized clinical trial of extended treatment to 3.6 years

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ABSTRACT

Background: Baricitinib, an oral selective Janus kinase inhibitor, improved clinical signs and symptoms of moderate-to-severe atopic dermatitis (AD) at week 16 in the phase 3 pediatric study BREEZE-AD-PEDS.

Objective: To assess longer-term efficacy and safety of baricitinib in pediatric patients aged 2 to <18 years.

Methods: In BREEZE-AD-PEDS long-term extension, responders and partial responders (validated Investigator Global Assessment-Atopic Dermatitis [vIGA-AD®] 0/1/2) at Week 16 remained on double-blind treatment to which they were randomized (placebo, baricitinib [1-mg equivalent, 2-mg equivalent, or 4-mg equivalent); non-responders (vIGA-AD 3 or 4) at Week 16 transitioned to open-label baricitinib 4-mg equivalent. Safety was summarized for all randomized patients who received ≥1 dose of study treatment.

Results: In total 467 patients received baricitinib for 750.7 patient-years. Proportion of responders/partial responders (at Week 16) who achieved vIGA-AD 0/1 at Week 52 was greater for baricitinib 4-mg equivalent (56.8%) versus all other treatment groups (42.2%, 47.7%, and 39.7% for 2-mg equivalent, 1-mg equivalent, and placebo, respectively). Most treatment-emergent adverse events were mild/moderate in severity. No deaths, pulmonary emboli, deep vein thromboses or arterial thrombotic events, major adverse cardiovascular events, malignancies, tuberculosis events, or gastrointestinal perforations were reported.

Conclusions: Baricitinib demonstrated sustained long-term efficacy. No new safety signals were identified.

Trial Registration: ClinicalTrials.gov Identifier: NCT03952559

ARTICLE HISTORY
Received 25 June 2024
Accepted 15 September 2024

KEYWORDS
Atopic dermatitis; pediatric; baricitinib

Introduction

Atopic dermatitis (AD) is one of the most common and chronic childhood diseases, occurring in approximately 9% of teenagers and up to 14% of children aged 0-4 years (1–3). Baricitinib, an oral selective Janus kinase (JAK) inhibitor (4) has received regulatory authorization in Europe, Japan, and several other countries for the treatment of moderate-to-severe AD in adults. European Guidelines for AD recommend (strong recommendation) baricitinib for the treatment of severe AD in adults (5). In the pediatric AD study BREEZE-AD-PEDS, baricitinib improved clinical signs and symptoms of moderate-to-severe AD in children and adolescents (6). Baricitinib received regulatory authorization in the European Union for patients ≥2 years with moderate-to-severe AD in October 2023 (7). Here we present longer-term safety and efficacy results from BREEZE-AD-PEDS.

Materials and methods

Study design and patients

The study design for the 16-week placebo-controlled period of BREEZE-AD-PEDS (ClinicalTrials.gov Identifier: NCT03952559), a multicenter, double-blind, randomized, placebo-controlled, phase 3 study, was previously described (6). Briefly, patients were randomized 1:1:1:1 to oral, once-daily placebo, baricitinib low, medium or high dose. Prior pharmacokinetic results showed that exposure to baricitinib 4-mg in patients aged 10 to <18 years was comparable to exposure in adults treated with baricitinib 4-mg; exposure to baricitinib 2-mg in patients aged 2 to <10 years was comparable to exposure in adults treated with baricitinib 4-mg (data on file). Baricitinib low, medium, and high doses, respectively, were 1-mg,

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/09546634.2024.2411834.
This article has been corrected with minor changes. These changes do not impact the academic content of the article.

2-mg, and 4-mg (tablets) for patients aged 10 to <18 years and 0.5-mg, 1-mg, and 2-mg (oral suspension) for patients aged 2 to <10 years. The long-term extension (LTE) treatment period is ongoing in 17 countries (Argentina, Australia, Austria, Brazil, Czech Republic, France, Germany, Hungary, India, Israel, Japan, Mexico, Poland, Russian Federation, Spain, Taiwan, United Kingdom). BREEZE-AD-PEDS started on May 24, 2019, with data presented through January 20, 2023. After the 16-week, placebo-controlled primary endpoint, patients continued long-term treatment for up 4 years (Figure S1). Responders and partial responders (patients who achieved a validated Investigator Global Assessment Atopic Dermatitis [vIGA-AD®] score of 0, 1, or 2 and never received rescue therapy) at week 16 continued the double-blind treatment to which they were initially randomized. After week 16, if patients lost response (vIGA-AD score increased to 3 or 4) they could transition to open-label baricitinib 4-mg equivalent based on their current age. Non-responders (week-16 vIGA-AD score of 3 or 4 or received rescue therapy) were transitioned to age-appropriate open-label baricitinib 4-mg equivalent. Patients from the pharmacokinetic lead-in study received open-label baricitinib 4-mg equivalent from study enrollment through the LTE.

During the first year of the LTE, use of background topical corticosteroids (TCSs; any strength), topical calcineurin inhibitors, and phosphodiesterase-4 inhibitors was allowed as prescribed by investigators. Patients could be rescued with phototherapy at investigator discretion and remained in the study but were required to temporarily interrupt study drug until phototherapy was completed. Patients rescued with systemic therapies (conventional systemics or biologics) were considered non-responders and discontinued from the study.

After year one of the LTE, treatment and transition to open-label baricitinib continued as in the first year. Voluntary interruptions of study drug (drug holidays) were allowed based on investigator discretion, patient/parent agreement, and at pre-defined response criteria (vIGA-AD score ≤2, <3% body surface area involvement, or ≥75% improvement in the Eczema Area and Severity Index [EASI]). BREEZE-AD PEDS was conducted in accordance with the ethical principles of the Declaration of Helsinki. The study was approved by the ethical review board at each participating site. Patient's parents or legal guardians provided written informed consent, and pediatric patients provided informed assent as required by ethical review boards prior to performing study procedures.

Patients were aged 2 to <18 years with a diagnosis of moderate-to-severe AD ≥12 months before screening if ≥6 years old or ≥6 months before screening if 2-5 years old. Moderate-to-severe AD diagnosis was based on vIGA-AD score ≥3, EASI score ≥16, and body surface area involvement ≥10% with a history of inadequate response to TCSs within the preceding 6 months and inadequate response or history of intolerance to topical calcineurin inhibitors or inadequate response to systemic treatments. Patients were excluded if they had a concomitant skin disease that would interfere with efficacy evaluations, adverse events associated with TCSs that would prevent their use as concomitant therapy, or concomitant illness requiring systemic corticosteroids.

Assessments

Efficacy assessments included the proportion of patients achieving vIGA-AD score 0 or 1, 75% improvement in the EASI (EASI75), and 75% improvement in the SCORing Atopic Dermatitis (SCORAD75).

Safety assessments included treatment-emergent adverse events (TEAEs), clinical laboratory tests, vital signs, and growth assessments. Radiographs of the hand, wrist, and fingers were collected to assess radiographic bone age and the difference between chronological age and radiographic bone age over time. For individual patients, a difference of ≥2 years between bone age and chronological age was considered outside the normal range (8). An unblinded independent data-monitoring committee external to the sponsor conducted regular reviews of safety findings. A blinded clinical event committee adjudicated potential cardiovascular events, arterial and venous thromboembolic events, and deaths.

Statistical analysis

Efficacy was assessed at Weeks 20, 24, 28, 40, and 52, and analyses were conducted on the intent-to-treat population (all randomly assigned patients in the double-blind treatment period). Results are presented using modified last observation carried forward with imputation per the prespecified analysis for the EASI75 and SCORAD75 and *post hoc* for vIGA-AD. Efficacy results are presented by treatment groups across the entire patient population (2 to <18 years).

Safety was summarized using descriptive statistics for all randomized patients who received ≥1 dose of study treatment and is reported for 2 populations:

- **Extended BARI population**: all patients randomly assigned who received ≥1 dose of baricitinib or placebo originally assigned in the placebo-controlled period. Data were censored after transition to open-label baricitinib.
- **All-BARI population**: all patients who received ≥1 dose of baricitinib at any time during the study, either during the pharmacokinetic lead-in or placebo-controlled periods, or after transitioning from placebo to baricitinib in the LTE.

Incidence rates (IRs) are reported per 100 patient-years at risk. For all study patients, dose-related trend for adverse events was defined as increasing IR with increasing dose (IR placebo < IR 1-mg equivalent < IR 2-mg equivalent < IR 4-mg equivalent).

Results

Baseline demographics and disease characteristics are presented in Table 1; patient disposition in Figure 1. In All-BARI, mean age was 11.9 years (71.3% ≥10 years); 50.5% of patients were female. Mean age at diagnosis was 2.6 years, mean duration of AD was 9.3 years, and 41.3% of patients had severe AD (baseline vIGA-AD 4). Overall, 467 patients were exposed to baricitinib (750.7 PY); 82.4% of patients ($n = 385$) had ≥52 weeks exposure and 29.1% ($n = 136$) had ≥2 years exposure. Median and maximum duration of exposure was 1.7 and 3.6 years, respectively (Table 2).

Efficacy

Among responders and partial responders at week 16 who remained on double-blind study drug, the proportion of patients achieving vIGA-AD 0 or 1 response was generally maintained from weeks 16-52. The proportion was greater for patients receiving baricitinib 4-mg equivalent (56.8%) versus other treatment groups at week 52 (42.2%, 47.7%, and 39.7% for 2-mg equivalent, 1-mg equivalent, and placebo, respectively) and at all timepoints (weeks 20-52; Figure 2). Patients who achieved EASI75 and SCORAD75 at

Table 1. Baseline patient demographics and disease characteristics.

	Extended Treatment				
	Placebo *N* = 123	BARI Low Dose (1-mg equivalent)[a] *N* = 120	BARI Medium Dose (2-mg equivalent)[a] *N* = 120	BARI High Dose (4-mg equivalent)[a] *N* = 120	All-BARI *N* = 467
Age, mean (SD), years	11.8 (4.0)	12.3 (4.1)	11.8 (3.7)	11.9 (3.8)	11.9 (3.9)
10 to <18 years, n (%)	89 (72.4)	87 (72.5)	86 (71.7)	88 (73.3)	333 (71.3)
6 to <10 years, n (%)	20 (16.3)	24 (20.0)	26 (21.7)	23 (19.2)	93 (19.9)
2 to <6 years, n (%)	14 (11.4)	9 (7.5)	8 (6.7)	9 (7.5)	40 (8.6)
Female, No. (%)	65 (52.8)	62 (51.7)	63 (52.5)	53 (44.2)	236 (50.5)
Race, No. (%)					
White	94 (76.4)	93 (77.5)	93 (77.5)	88 (73.3)	347 (74.3)
Asian	17 (13.8)	18 (15.0)	18 (15.0)	21 (17.5)	85 (18.2)
Black	3 (2.4)	2 (1.7)	5 (4.2)	4 (3.3)	12 (2.6)
Geographic region, N (%)					
Europe	46 (37.4)	45 (37.5)	43 (35.8)	46 (38.3)	166 (35.5)
Japan	9 (7.3)	10 (8.3)	10 (8.3)	9 (7.5)	35 (7.5)
Rest of world[b]	68 (55.3)	65(54.2)	67(55.8)	65(54.2)	266(57.0)
Age at AD diagnosis, mean (SD), years	2.6 (3.6)	2.6 (3.9)	2.5 (3.5)	3.0 (4.0)	2.6 (3.7)
Duration since AD diagnosis, mean (SD), years	9.2 (4.4)	9.8 (5.1)	9.4 (4.2)	9.0 (4.1)	9.3 (4.5)
Height percentile, mean (SD)	46.2 (29.9)	47.2 (27.5)	46.8 (30.3)	51.2 (29.3)	48.1 (28.6)
Weight percentile, mean (SD)	58.8 (31.9)	56.6 (31.5)	56.1 (30.1)	66.4 (28.5)	59.5 (30.3)
BMI percentile, mean (SD)	63.4 (30.7)	60.3 (32.1)	61.4 (28.3)	70.0 (26.4)	63.6 (29.1)
vIGA-AD, No. (%)					
3	75 (61.0)	75 (62.5)	74 (61.7)	75 (62.5)	274 (58.7)
4	48 (39.0)	45 (37.5)	46 (38.3)	45 (37.5)	193 (41.3)
EASI score, mean (SD)	26.9 (10.3)	26.6 (10.0)	26.8 (9.0)	25.3 (9.5)	27.1 (10.1)
% BSA affected by AD, mean (SD)	41.2 (19.0)	42.4 (19.5)	41.2 (16.8)	40.4 (17.7)	42.7 (19.0)
SCORAD, mean (SD)	61.3 (12.0)	63.6 (12.7)	62.4 (11.8)	60.7 (13.1)	62.8 (12.8)
Prior TCNI use, No. (%)	98 (79.7)	106 (88.3)	102 (85.0)	105 (87.5)	398 (85.2)
Prior TCS use, No. (%)	122 (99.2)	118 (98.3)	120 (100)	118 (98.3)	463 (99.1)

AD: atopic dermatitis; BARI: baricitinib; BMI: body mass index; BSA: body surface area; EASI: Eczema Area Severity Index; N: number of participants in analysis set; n: number of participants in the specified category; vIGA-AD: validated Investigator Global Assessment-Atopic Dermatitis; SD: standard deviation; SCORAD: SCORing Atopic Dermatitis; TCNI: topical calcineurin inhibitor; TCS: topical corticosteroid.
[a]For patients aged 10 to <18 years: BARI low dose = 1 mg; BARI medium dose = 2 mg, and BARI high dose = 4 mg; for patients aged 2 to <10 years: BARI low dose = 0.5 mg, BARI medium dose = 1 mg, and BARI high dose = 2 mg.
[b]Rest of the world included Argentina, Australia, Israel, Russia, Taiwan, Brazil, India, and Mexico.

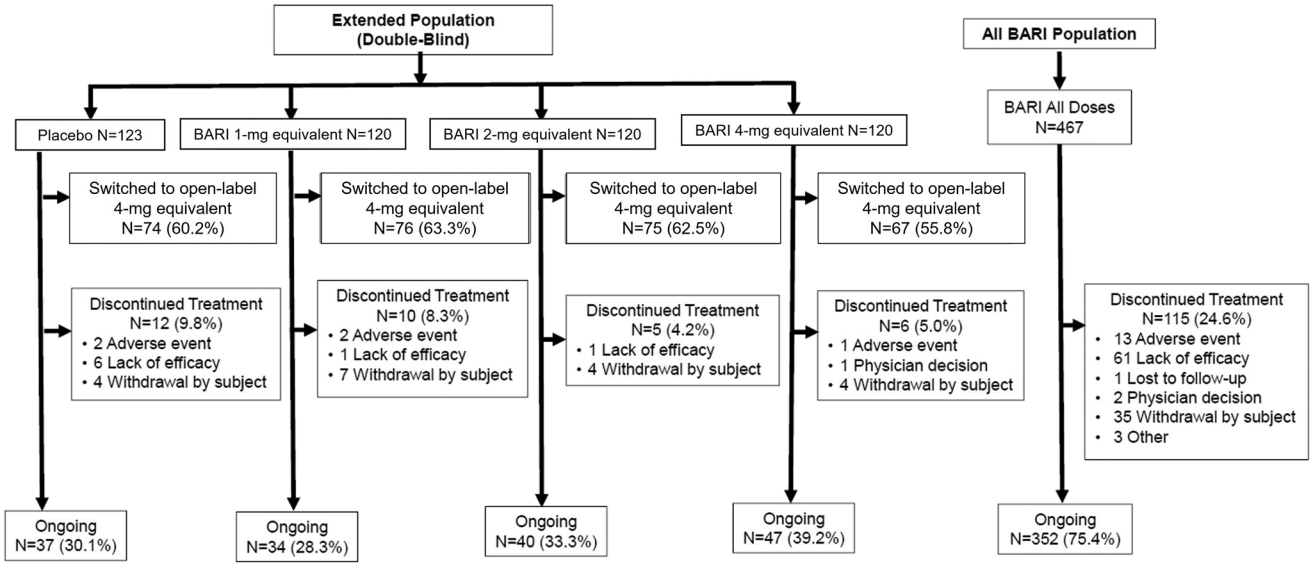

Figure 1. CONSORT diagram for patients in the long-term period of BREEZE-AD-PEDS as responders or partial responders. BARI: baricitinib.

week 52 generally maintained control from weeks 16-52, especially patients receiving baricitinib 4-mg equivalent versus those in other treatment groups (Figure 2). Use of high/ultra-high potency TCSs after week 16 was similar between treatment groups, with ≤6% of baricitinib-treated patients and 10% of placebo-treated patients using higher potency TCSs.

Safety

Treatment-emergent adverse events

In All-BARI, 362 patients reported ≥1 TEAE with no dose-related trend in IR in Extended BARI overall (Table 2) or by age group (Table S1). The most common TEAE System Organ Class was

Table 2. Treatment exposure and safety summary.

	No. (%) [IR]				
	Extended Treatment				
	Placebo *N* = 123	BARI 1-mg equivalent[a] *N* = 120	BARI 2-mg equivalent[a] *N* = 120	BARI 4-mg equivalent[a] *N* = 120	All-BARI *N* = 467
Patient-Years of Exposure	102.9	99.5	103.6	121.6	750.7
Patients with ≥52 weeks, No. (%)	41 (33.3)	43 (35.8)	45 (37.5)	57 (47.5)	385 (82.4)
Patient with ≥76 weeks, No. (%)	30 (24.4)	26 (21.7)	30 (25.0)	39 (32.5)	279 (59.7)
Patient with ≥104 weeks, No. (%)	12 (9.8)	12 (10.0)	12 (10.0)	14 (11.7)	136 (29.1)
Median duration, weeks	17	18	19	40	87
Longest exposure, weeks	143	134	140	144	185
Any TEAE	76 (61.8) [150.2]	76 (63.3) [148.3]	69 (57.5) [135.1]	78 (65.0) [133.7]	362 (77.5) [125.3]
TEAE severity					
Mild	35 (28.5) [46.1]	45 (37.5) [65.6]	39 (32.5) [51.3]	38 (31.7) [40.2]	168 (36.0) [30.5]
Moderate	34 (27.6) [40.2]	28 (23.3) [32.4]	26 (21.7) [30.5]	35 (29.2) [35.8]	166 (35.5) [28.9]
Severe	7 (5.7) [7.0]	3 (2.5) [3.0]	4 (3.3) [3.9]	5 (4.2) [4.3]	28 (6.0) [3.8]
Serious adverse events	7 (5.7) [7.1]	2 (1.7) [2.0]	3 (2.5) [2.9]	4 (3.3) [3.4]	31 (6.6) [4.2]
Permanent Discontinuation of Study Treatment because of an AE	2 (1.6) [1.9]	2 (1.7) [2.0]	0	2 (1.7) [1.7]	13 (2.8) [1.7]
Deaths	0	0	0	0	0
Infections					
Treatment-emergent infections	45 (36.6) [63.3]	50 (41.7) [68.2]	47 (39.2) [63.8]	54 (45.0) [60.7]	284 (60.8) [64.4]
Serious infections[b]	2 (1.6) [2.0]	0	1 (0.8) [1.0]	2 (1.7) [1.7]	11 (2.4) [1.5]
Infections leading to permanent study discontinuation	1 (0.8) [1.0]	1 (0.8) [1.0]	0	0	5 (1.1) [0.7]
Herpes zoster	1 (0.8) [1.0]	2 (1.7) [2.0]	0	1 (0.8) [0.8]	7 (1.5) [0.9]
Herpes simplex[c]	4. (3.3) [3.9]	4. (3.3) [4.1]	2 (1.7) [1.9]	4. (3.3) [3.4]	28 (6.0) [3.9]
Tuberculosis	0	0	0	0	0
Opportunistic excluding tuberculosis	0	0	0	1 (0.8) [0.8]	1 (0.2) [0.1]
Skin infections requiring antibiotic infections	8 (6.5) [8.2]	8 (6.7) [8.2]	9 (7.5) [9.0]	5 (4.2) [4.1]	52 (11.1) [7.3]

AE: adverse event; BARI: baricitinib; IR: incident rate; N: number of participants in analysis set; TEAE: treatment-emergent adverse event.
[a]For patients aged 10 to <18 years: BARI low dose = 1 mg; BARI medium dose = 2 mg, and BARI high dose = 4 mg; for patients aged 2 to <10 years: BARI low dose = 0.5 mg, BARI medium dose = 1 mg, and BARI high dose = 2 mg.
[b]See Table S3 for complete list of SAEs.
[c]Herpes simplex included the preferred terms of herpes simplex, oral herpes, eczema herpeticum, and ophthalmic herpes simplex.

infections (All-BARI IR, 64.4), and the most common TEAE Preferred Terms were COVID-19, nasopharyngitis, acne, and headache (Table 3); the majority of TEAEs were mild to moderate in severity (92.3% in All-BARI) (Table 2). Among severe TEAEs, no dose-related trend was observed in Extended BARI (Table 2; Table S2). Cases of acne were reported in adolescents (mean age 15.2 years, range 11-19 years), were mostly mild (41/51, 80.4% in All-BARI) and most were treated with topical therapies. No cases of severe acne were reported in any treatment group, and no patients discontinued treatment due to acne. In All-BARI, 6.6% ($n = 31$) of patients reported ≥1 serious adverse event (SAE; IR 4.2); no dose-related trend was observed in Extended BARI overall (Table 2) or by age group (Table S1). SAEs reported by more than one patient in All-BARI were ophthalmic herpes simplex ($n = 2$), herpes simplex ($n = 2$), asthma ($n = 2$), and atopic dermatitis ($n = 3$); all SAEs are presented in Table S3. There were no deaths in the study. The discontinuation rate due to adverse events in All-BARI was low (IR = 1.7), with no dose-related trend in Extended BARI overall (Table 2) or by age group (Table S1). Adverse events leading to discontinuation were suicide attempt and ophthalmic herpes simplex in the placebo group, herpes zoster and myalgia in the baricitinib 1-mg equivalent group, and headache ($n = 3$), atopic dermatitis ($n = 2$), and one each of lichen planus, respiratory tract infection, eczema impetiginous, herpes simplex, herpes zoster, and urticaria in the baricitinib 4-mg equivalent group. Of these events, suicide attempt, both cases of atopic dermatitis, eczema impetiginous, and herpes simplex were SAEs.

Adverse events of special interest

The most frequently reported infections in All-BARI were COVID-19, nasopharyngitis, and upper respiratory tract infections (Table 3). In All-BARI, 5 patients reported infections that led to treatment discontinuation (IR 0.7): herpes zoster ($n = 2$), eczema impetiginous ($n = 1$), herpes simplex ($n = 1$), and respiratory tract infection ($n = 1$); there was no dose-related trend in Extended BARI. The All-BARI IR for SAE infections was 1.5 ($n = 11$), with no dose-related trend in Extended BARI (Table 2). The most reported serious infections in All-BARI were herpes simplex ($n = 2$) and ophthalmic herpes simplex ($n = 2$). COVID-19 was reported as an SAE in 2 patients (1 placebo and 1 All-BARI receiving baricitinib 4-mg equivalent) (Table S3); both were treated with systemic steroids, recovered, and continued in the study. No events of tuberculosis were reported.

Herpes zoster was reported in 7 patients (IR 0.93) in All-BARI and 1 patient in the placebo group, with no dose-related trend in Extended BARI (Table 2). All cases were uncomplicated with no ocular, visceral, or motor nerve involvement; all resolved with antiviral treatment and no cases were SAEs. One case in the baricitinib 4-mg equivalent group was disseminated (non-SAE), affecting 5 dermatomes, and was considered to be an opportunistic infection. The patient recovered with antiviral treatment and continued in the study. This was the only opportunistic infection reported. All other herpes zoster cases were mild to moderate in severity, localized, or non-multidermatomal infections that were treated with antiviral medication and resolved. The All-BARI IR of herpes simplex was 3.9 ($n = 28$), with no dose-related trend in Extended BARI. Three patients receiving baricitinib 4-mg equivalent reported eczema herpeticum (moderate severity in 2 patients and 1 patient who reported mild events on 2 occasions).

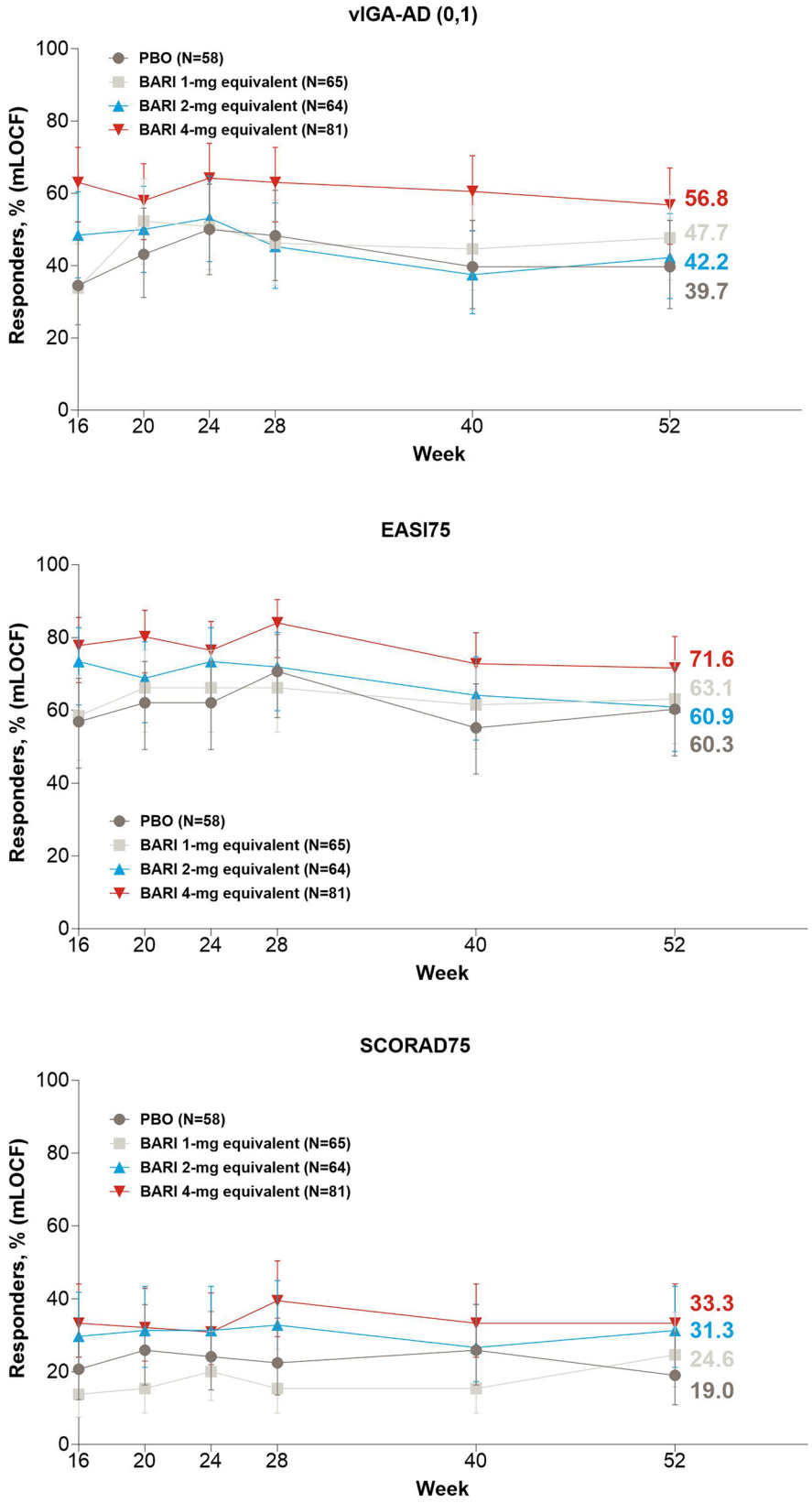

Figure 2. Efficacy outcomes over time in responders/partial responders at Week 16. BARI: baricitinib; EASI: Eczema Area Severity Index; mLOCF: modified last observation carried forward; PBO: placebo; SCORAD: SCORing Atopic Dermatitis; vIGA-AD: validated Investigator Global Assessment-Atopic Dermatitis.

No pulmonary emboli, deep vein thromboses, arterial thrombotic events, major adverse cardiovascular events, malignancies, or gastrointestinal perforations were reported.

Growth

Mean height, weight, and body mass index changes in Z-scores (standard deviation score) remained at or close to 0 through

Table 3. Treatment-emergent adverse events reported in ≥2% of patients in the All-BARI group.

	No. (%) [IR]				
	Extended Treatment				
	Placebo *N* = 123	BARI 1-mg equivalent[a] *N* = 120	BARI 2-mg equivalent[a] *N* = 120	BARI 4-mg equivalent[a] *N* = 120	All-BARI *N* = 467
COVID-19	6 (4.9) [6.1]	8 (6.7) [8.4]	12 (10.0) [12.9]	14 (11.7) [12.5]	88 (18.8) [12.8]
Nasopharyngitis	9 (7.3) [9.3]	9 (7.5) [9.4]	7 (5.8) [7.2]	9 (7.5) [7.7]	66 (14.1) [9.6]
Acne	6 (4.9) [6.0]	6 (5.0) [6.6]	5 (4.2) [5.1]	12 (10.0) [10.4]	51 (10.9) [7.4]
Headache	10 (8.1) [9.9]	7 (5.8) [7.4]	12 (10.0) [12.7]	12 (10.0) [10.6]	46 (9.9) [6.5]
Upper respiratory tract infection	4 (3.3) [3.9]	5 (4.2) [5.2]	7 (5.8) [7.0]	7 (5.8) [5.8]	43 (9.2) [6.0]
Pyrexia	2 (1.6) [1.9]	5 (4.2) [5.1]	6 (5.0) [6.0]	4 (3.3) [3.3]	34 (7.3) [4.7]
Abdominal Pain	4 (3.3) [3.9]	3 (2.5) [3.1]	7 (5.8) [7.1]	8 (6.7) [7.0]	26 (5.6) [3.5]
Influenza	4 (3.3) [4.0]	0	2 (1.7) [2.0]	6 (5.0) [5.1]	23 (4.9) [3.1]
Pharyngitis	1 (0.8) [1.0]	5 (4.2) [5.2]	6 (5.0) [5.9]	3 (2.5) [2.5]	22 (4.7) [3.0]
Bronchitis	5 (4.1) [4.9]	8 (6.7) [8.3]	1 (0.8) [1.0]	4 (3.3) [3.4]	20 (4.3) [2.7]
Asthma	4 (3.3) [3.9]	1 (0.8) [1.0]	5 (4.2) [4.9]	4 (3.3) [3.4]	19 (4.1) [2.6]
Blood creatine phosphokinase increased	1 (0.8) [1.0]	1 (0.8) [1.0]	1 (0.8) [1.0]	2 (1.7) [1.7]	18 (3.9) [2.4]
Cough	4 (3.3) [3.9]	2 (1.7) [2.0]	3 (2.5) [3.0]	5 (4.2) [4.2]	16 (3.4) [2.1]
Diarrhoea[b]	2 (1.6) [1.9]	1 (0.8) [1.0]	2 (1.7) [1.9]	6 (5.0) [5.1]	16 (3.4) [2.2]
Vomiting	3 (2.4) [2.9]	2 (1.7) [2.0]	3 (2.5) [2.9]	1 (0.8) [0.8]	16 (3.4) [2.1]
Gastroenteritis	2 (1.6) [1.9]	0	3 (2.5) [2.9]	4 (3.3) [3.4]	15 (3.2) [2.0]
Herpes simplex	2 (1.6) [1.9]	1 (0.8) [1.0]	1 (0.8) [1.0]	1 (0.8) [0.8]	15 (3.2) [2.0]
Impetigo	5 (4.1) [5.0]	1 (0.8) [1.0]	3 (2.5) [2.9]	2 (1.7) [1.6]	15 (3.2) [2.0]
Rhinitis	1 (0.8) [1.0]	4 (3.3) [4.1]	1 (0.8) [1.0]	4 (3.3) [3.3]	14 (3.0) [1.9]
Abdominal pain upper	1 (0.8) [1.0]	3 (2.5) [3.0]	2 (1.7) [2.0]	4 (3.3) [3.3]	12 (2.6) [1.6]
Arthralgia	0	4 (3.3) [4.2]	2 (1.7) [1.9]	0	12 (2.6) [1.6]
Folliculitis	2 (1.6) [2.0]	1 (0.8) [1.0]	0	3 (2.5) [2.5]	12 (2.6) [1.6]
Dysmenorrhoea[c]	3 (4.6) [5.7]	1 (1.6) [1.8]	3 (4.8) [5.5]	0	6 (2.5) [1.6]
Oral herpes	2 (1.6) [1.9]	3 (2.5) [3.1]	1 (0.8) [1.0]	1 (0.8) [0.8]	11 (2.4) [1.5]
Skin infection	1 (0.8) [1.0]	3 (2.5) [3.0]	1 (0.8) [1.0]	1 (0.8) [0.8]	11 (2.4) [1.5]
Tonsillitis	2 (1.6) [1.9]	2 (1.7) [2.0]	0	0	10 (2.1) [1.3]

BARI: baricitinib; IR: incident rate; COVID-19 : coronavirus disease 2019; N: number of participants in analysis set.
[a]For patients aged 10 to <18 years: BARI low dose = 1 mg; BARI medium dose = 2 mg, and BARI high dose = 4 mg; for patients aged 2 to <10 years: BARI low dose = 0.5 mg, BARI medium dose = 1 mg, and BARI high dose = 2 mg.
[b]Nausea was reported <2% of pts in All-BARI (3 [2.4%], 1 [0.8%], 2 [1.7%], 2 [1.7%], 9 [1.9%] of patients in the placebo, baricitinib 1-mg equivalent, baricitinib 2-mg equivalent, baricitinib 4-mg equivalent, and All-BARI respectively).
[c]Denominator and patient-years adjusted because event is specific to females: *N* = 65 (placebo), *N* = 62 (baricitinib 1-mg equivalent), *N* = 63 (baricitinib 2-mg equivalent), *N* = 53 (baricitinib 4-mg equivalent), *N* = 236 (All-BARI).

136 weeks of the study (Figure S2), which is consistent with patients maintaining a growth velocity aligned with their average baseline Z-score (compared to age- and sex-matched peers). Imaging results (hand radiography) showed that the mean difference between chronological age and bone age remained similar to the baseline difference and on average was <2 years (Table S4). These results suggest that on average, radiographic bone age (related to growth plate closure) remained consistent with chronological age for patients aged 2 to <18 years through week 124.

Bone alkaline phosphatase (ALP) was collected as a reflex test if the ALP result was >2x upper limit of normal (ULN). Treatment-emergent elevations in ALP (>2x ULN) occurred in 10 patients (placebo *n* = 2; All-BARI *n* = 8) and did not occur concurrently with clinically relevant elevations of other liver enzymes (alanine transaminase, aspartate aminotransferase, and gamma-glutamyl transferase) or total bilirubin and were associated with elevated bone ALP in all cases where tested (8/10). The elevations in ALP appear to be related to normal physiological growth processes (childhood or pubertal growth spurt). Four younger patients (baseline age 3-6 years) with elevated ALP grew 7-11 cm in 18-24 months during the study (average expected growth for this age is 5-8 cm/year) (9). Four older patients (baseline age 10-12 years) with elevated ALP grew 7-15 cm in 24 months during the study (average expected growth for this age is 4-9 cm/year) (9). One patient with menarche prior to ALP elevation (baseline age 13 years) grew 4 cm in 2 years during the study, and one male patient (baseline age 12 years) did not show any growth after 4 months in the study and discontinued prior to any subsequent assessments.

Laboratory results

Categorical shifts to clinically relevant abnormal values for select laboratory analytes (hepatic, creatine phosphokinase [CPK], renal, and hematological) were similar across treatment groups in Extended BARI, except lipids (total cholesterol, high-density lipoprotein, and low-density lipoprotein), for which dose-related trends were observed (Table S5). No patients discontinued treatment due to elevated cholesterol levels, and no cholesterol-lowering medication (statin) use was reported for any patient. In All-BARI, 38.7% (*n* = 179) of patients experienced an elevation in CPK (IR 23.85); no dose-related trends were observed in Extended BARI. Most CPK increases were increases to Common Terminology Criteria for Adverse Events (CTCAE) Grades 1 and 2. Elevations of CPK >2.5x ULN (CTCAE grade ≥2) were not associated with adverse events indicative of muscle injury (myalgia), and in almost all cases, investigators attributed the increased CPK to physical or athletic activity. For hepatic laboratory abnormalities, no dose-related trends were observed and no patients permanently discontinued treatment due to laboratory abnormality or met laboratory criteria for Hy's law.

Discussion

Primary results from BREEZE-AD-PEDS showed that in children and adolescents with moderate-to-severe AD, baricitinib 4-mg equivalent was superior to placebo with respect to the primary and key secondary efficacy outcomes at week 16, and the safety profile was consistent with the established safety profile of baricitinib in adults (6). This is the first report of longer-term efficacy and safety in baricitinib-treated pediatric patients with moderate-to-severe AD, and baricitinib demonstrated sustained long-term efficacy and no new safety signals.

Efficacy response among pediatric patients who were vIGA-AD responders and partial responders and remained on double-blind treatment was generally maintained to week 52 and was greater for patients receiving baricitinib 4-mg equivalent versus all other treatment groups. These efficacy results were consistent with those in a similar analysis of baricitinib-treated adult patients with moderate-to-severe AD (10).

In the safety analysis, there were no dose-related trends in IRs for SAEs, reports of TEAEs, discontinuations due to adverse events, or reports of treatment-emergent infection. The profile of TEAEs over longer-term baricitinib exposure (751 PY) in pediatric AD patients in this study was similar to that observed in adults with 2247 PY exposure (11). In All-BARI in this study, IRs for infections and serious infections (64.4 and 1.5, respectively) were comparable to those reported in adults (91.7 and 2.1, respectively). As expected for pediatric AD patients, IRs for herpes zoster and herpes simplex (0.9 and 3.9, respectively) were lower than those for adults (2.3 and 10.3, respectively). Incidence rates for headache, diarrhea, and upper abdominal pain were similar between pediatric AD patients (6.5, 2.2, and 1.6, respectively) and adult AD patients (7.6, 3.5, and 1.8, respectively); however, abdominal pain, vomiting, and gastroenteritis were reported in ≥2% of pediatric patients but in <2% of adults. As expected, the IR for acne was higher (7.4) in this study including adolescents than in adults (IR 3.3) (12). In this study, most cases of acne in All-BARI were mild and no severe cases were reported; most cases were treated with topical therapies, and no patients discontinued study treatment due to acne. Dose-related trends were seen for increases in total and low-density lipoprotein cholesterol and a near dose-related trend was seen for increases in high-density lipoprotein cholesterol. Dose-related trends for increases in cholesterol have also been observed in baricitinib-treated adults (11, 13), and all patients (including pediatric patients) should be managed appropriately according to guidelines for hyperlipidemia. No pulmonary emboli, deep vein thromboses, or arterial thrombotic events, major adverse cardiovascular events, malignancies, tuberculosis, or gastrointestinal perforations were reported.

Atopic dermatitis may be associated with poor bone health (14). Additionally, per the International Conference on Harmonization (ICH) guidelines (ICH Efficacy Guidelines) (15) and due to effects on bone growth reported for JAK inhibitors (16) and potential effects on growth in children and adolescents, physical growth including height, weight, and body mass index was carefully monitored throughout this pediatric study. Continued assessment of physical growth during the LTE treatment period of the current study revealed no clinically meaningful observations related to baricitinib treatment. Patients on average maintained growth velocity at a rate comparable to healthy age- and sex-matched peers (9). Imaging results were consistent with physical growth results, with small mean differences over time between chronological age and bone age (generally within 0.5 years). Recent analysis has suggested that dupilumab may increase bone mineralization markers, including bone ALP in children (17). While we only collected bone ALP as a reflex test if ALP was elevated, our results suggest that elevated ALP was associated with elevated bone ALP and related to childhood or pre-pubertal growth spurts.

This study has limitations. It was not specifically designed to assess long-term efficacy. After the 16-week primary endpoint, patients were allowed to use TCSs (any strength) as prescribed by their study doctor. Use of high/ultrahigh potency TCSs can confound the interpretation of the efficacy results, but in the current study TCS use was reported in similar proportions of baricitinib- and placebo-treated patients. Additionally, while IRs provide an estimate of the number of patients experiencing an event per 100 PY and can be viewed in context with IRs from the literature, 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.

Conclusions

In BREEZE-AD PEDS, baricitinib demonstrated sustained long-term efficacy in children and adolescents with moderate-to-severe AD. The safety profile was consistent with the established safety profile for baricitinib in adults with moderate-to-severe AD, with no new safety signals identified. These results suggest that the benefit-risk profile for baricitinib in pediatric patients remains favorable during longer-term treatment.

Acknowledgments

The authors would like to thank the investigators and patients who have participated in this baricitinib atopic dermatitis clinical trial. The authors would also like to acknowledge Kathy Oneacre, MA (Syneos Health, Morrisville, NC, USA) who provided medical writing support and Raena Fernandes (Syneos Health, Morrisville, NC, USA) who provided editing support that was funded by Eli Lilly and Company.

Authors' contributions

Andreas Wollenberg, Lawrence F Eichenfield, Marieke M.B. Seyger, Marco Pontes and Amy Paller contributed to the interpretation of data and critical review of the manuscript for important intellectual content; Masanori Ikeda and Chia-Yu Chu contributed to the acquisition and interpretation of data, and critical review of the manuscript for important content; Apurva Prakash contributed to the conception, design, acquisition, analysis and interpretation of the data, drafting of the manuscript, and critical review of the manuscript for important intellectual content; Robinette Angle contributed to the analysis and interpretation of data and critical review of the manuscript for important intellectual content, Danting Zhu contributed to the acquisition, analysis and interpretation of data and critical review of the manuscript for important intellectual content.

Disclosure statement

Andreas Wollenberg reports receiving grants, consulting fees and/or study support from Abbvie, Aileens, Almirall, Beiersdorf, Galapagos, Galderma, Glenmark, GSK, Janssen, LEO. Pharma, Eli Lilly, L'Oreal, MedImmune, MSD, Novartis, Pfizer, Pierre Fabre, Regeneron, Sanofi and UCB. Masanori Ikeda reports receiving a scholarship donation from the Central Research Institute of Pias; participating in clinical studies and/or receiving honoraria as a speaker/consultant for AbbVie, AstraZeneca, Eli Lilly, GlaxoSmithKline, Hisamitsu, Maruho, MedImmune, Novo Nordisk,

Pfizer, Sanofi, and Yanssen Pharmaceutical. Chia-Yu Chu reports being a consultant for AbbVie, Amgen, Eli Lilly, Jassen, Novartis, Pfizer, Roche, Sanofi, United BioPharma, and Viatris; a speaker for AbbVie, Eli Lilly, GlaxoSmithKline, Jassen, Novartis, Pfizer, Roche, Sanofi, United BioPharma, and Viatris; an investigator for AbbVie, Amgen, Dermira, Eli Lilly, Novartis, Oneness Biotech, Pfizer, Regeneron, Roche, Sanofi, and United BioPharma, and receiving grants from Novartis, Jassen, Regeneron, and Sanofi. Lawrence F. Eichenfield reports serving as a scientific adviser, consultant, and/or clinical study investigator for AbbVie, Almirall, Amryt, Aslan, Arcutis, Arena, Castle Biosciences, Dermavant, Eli Lilly and Company, Forté, Galderma, Incyte, LEO, Novartis, Ortho Dermatologics, Pfizer, Regeneron, and Sanofi Genzyme. Marieke M.B. Seyger received grants from/was involved in clinical trials for Abbvie, Amgen, Celgene, Eli-Lilly, Janssen, Leo Pharma, Pfizer; served as consultant for Abbvie, BMS, Eli Lilly, Janssen, Leo Pharma, Novartis, Pfizer, UCB; fees were paid directly to the institution. Apurva Prakash, Robinette Angle, Danting Zhu, and Marco Pontes are employees and stockholders of Eli Lilly and Co. Amy S. Paller reports being an investigator for AbbVie, Applied Pharma Research, Dermavant, Eli Lilly, Incyte, Janssen, Krystal, Regeneron, UCB; Consultant for Aegerion Pharma, Azitra, BioCryst, Boehringer-Ingelheim, Bristol Myers Squibb, Eli Lilly, Janssen, Johnson & Johnson, Krystal, LEO Pharma, Novartis, Primus, Regeneron, Sanofi/Genzyme, Seanergy, TWI Biotechnology, UCB; and on the Data Safety Monitoring Board for AbbVie, Abeona, Catawba, Galderma, InMed.

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.

Funding

Baricitinib is developed by Eli Lilly and Company, under license from Incyte Corporation. Eli Lilly and Company (Indianapolis, IN, USA) was involved in the study design, data collection, data analysis, data interpretation, manuscript preparation, and publication decisions. All authors had full access to all data in the study and had final responsibility for the decision to submit for publication.

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