Safety of Baricitinib for the Treatment of Atopic Dermatitis in Pediatric Patients Aged 2 to Less Than 18 Years

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BACKGROUND

- Baricitinib, an oral selective JAK inhibitor, is approved in Europe, Japan, and multiple other countries for the treatment of moderate-to-severe AD in adults who are candidates for systemic therapy[1]
- BREEZE-AD-PEDS (NCT03952559) is a Phase 3, randomized, double-blind, placebo-controlled trial of children and adolescents with moderate-to-severe AD who have inadequate response or intolerance to topical therapy
  - The primary efficacy results have been previously presented[2]

OBJECTIVE

- To report longer-term safety data for baricitinib in pediatric patients (aged ≥2 to <18 years) with moderate-to-severe AD
  - All patients had completed ≥6 months of treatment unless they discontinued early from the study

SUMMARY OF KEY FINDINGS

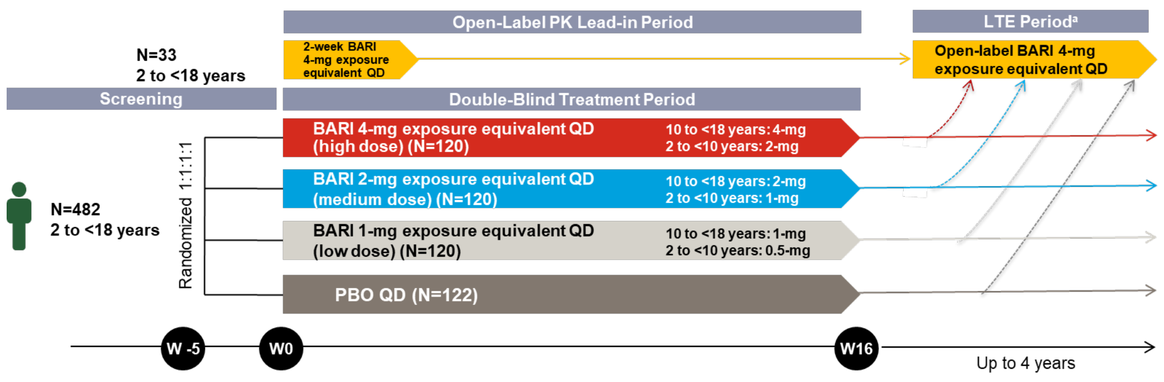
- A total of 466 pediatric patients received baricitinib for 533.6 patient-years (maximum exposure ~3 years)
- The majority of TEAEs were mild-to-moderate in severity
- Discontinuation rate due to AEs in the All-BARI population was low (IR=1.9)
- Growth assessments showed patients maintained a growth velocity consistent with their baseline height, weight, or BMI percentile
- 1 opportunistic infection (herpes zoster) was reported
  - This was a disseminated herpes zoster infection affecting 5 dermatomes; the participant recovered with antiviral treatment and continued in the study

CONCLUSIONS

- This initial safety analysis in pediatric patients with moderate-to-severe AD shows the safety profile was generally consistent with the established safety profile for baricitinib in adults with moderate-to-severe AD[3]
- Growth assessments over the course of treatment showed that participants maintained a growth velocity consistent with their baseline height, weight, or BMI percentile
- No new safety signals were identified in the pediatric population
- No deaths, pulmonary embolisms, deep vein thromboses, arterial thrombotic events, major adverse cardiovascular events, malignancies, tuberculosis events, or gastrointestinal perforations were reported

METHODS

STUDY DESIGN: BREEZE-AD-PEDS



[a] Patients transitioned to open-label BARI high dose after Week 16 based on response criteria (non-responders transitioned to open-label drug); responders and partial responders to double-blind treatment remained on the double-blind treatment to which they were responding

Safety Analyses

- Results are reported for 2 populations:
  - Extended BARI: Patients who were continuously treated from baseline with low, medium, and high doses of BARI (1-mg, 2-mg, or 4-mg exposure equivalents, respectively) and censored after transition to open-label BARI
    - This population allows assessment of dose response for safety outcomes during longer-term treatment
  - All-BARI: Patients who received any BARI dose at any time during the study (ie, greatest BARI exposure)
- The proportions of patients with events and IR/100 patient-years at risk were calculated
  - IR is 100× the number of patients experiencing the AE divided by the event-specific exposure to treatment (exposure time up to the first event for patients with the event and exposure time to the end of the period for patients without the event, in years)

RESULTS

Patient Demographics[a]

	All-BARI Population (N=466)
Age, years, mean (SD)	11.9 (3.9)
Female, n (%)	235 (50.4)
Race, n (%)	
White	346 (74.2)
Asian	85 (18.2)
Other	21 (4.5)
Weight percentile, mean (SD)	58.9 (30.3)
Height percentile, mean (SD)	48.1 (28.6)
BMI percentile, mean (SD)	63.6 (29.1)
Geographic region, n (%)	
Europe	166 (35.6)
Japan	35 (7.5)
Rest of the world	265 (56.9)

[a] Data cut-off was June 20, 2022

Overview of AEs in the Extended BARI and All-BARI Populations[a]

- Worsening AD (n=3), herpes simplex (n=2), and ophthalmic herpes simplex (n=2) were the most frequently reported serious AEs in the All-BARI population

	Extended BARI Population				
n (%) [IR]	PBO (N=122), PYE=79.9	BARI 1-mg Exposure Equivalent (N=120), PYE=78.6	BARI 2-mg Exposure Equivalent (N=120), PYE=79.1	BARI 4-mg Exposure Equivalent (N=120), PYE=91.1	All-BARI Population (N=466), PYE=533.6
Any TEAE	73 (59.8) [169.0]	71 (59.2) [156.6]	68 (56.7) [158.6]	71 (59.2) [148.4]	326 (70.0) [139.5]
TEAE severity					
Mild	35 (28.7) [57.4]	41 (34.2) [71.3]	40 (33.3) [68.9]	35 (29.2) [48.7]	161 (34.5) [40.9]
Moderate	31 (25.4) [45.9]	27 (22.5) [38.1]	26 (21.7) [38.7]	31 (25.8) [40.6]	145 (31.1) [34.2]
Severe	7 (5.7) [9.0]	3 (2.5) [3.8]	2 (1.7) [2.5]	5 (4.2) [5.7]	20 (4.3) [3.8]
Serious AEs	7 (5.7) [9.0]	2 (1.7) [2.5]	1 (0.8) [1.3]	4 (3.3) [4.5]	22 (4.7) [4.2]
Discontinuation of study treatment because of an AE[b]	2 (1.6) [2.5]	2 (1.7) [2.5]	0	1 (0.8) [1.1]	10 (2.1) [1.9]

[a] Data cut-off was June 20, 2022; [b] AEs that led to discontinuation in the PBO population were suicide attempt and ophthalmic herpes simplex; AEs that led to discontinuation in the All-BARI population were herpes zoster (n=2), dermatitis atopic (n=2), headache (n=2), lichen planus, urticaria, respiratory tract infection, and myalgia

TEAEs in the Extended BARI and All-BARI Populations[a]

- No dose-related trends in IR of the most frequently reported TEAEs were observed

	Extended BARI Population				
n (%) [IR]	PBO (N=122), PYE=79.9	BARI 1-mg Exposure Equivalent (N=120), PYE=78.6	BARI 2-mg Exposure Equivalent (N=120), PYE=79.1	BARI 4-mg Exposure Equivalent (N=120), PYE=91.1	All BARI Population (N=466), PYE=533.6
Patients with ≥1 TEAE of infection[b]	46 (37.7) [78.4]	44 (36.7) [69.7]	44 (36.7) [72.6]	45 (37.5) [62.2]	242 (51.9) [69.6]
TEAEs reported in ≥3% of patients in All-BARI population					
COVID-19	6 (4.9) [7.7]	7 (5.8) [9.1]	11 (9.2) [14.8]	12 (10.0) [13.7]	70 (15.0) [13.8]
Nasopharyngitis	9 (7.4) [11.9]	7 (5.8) [9.1]	6 (5.0) [7.9]	7 (5.8) [7.9]	50 (10.7) [10.0]
Acne	6 (4.9) [7.7]	6 (5.0) [8.2]	5 (4.2) [6.6]	7 (5.8) [7.9]	41 (8.8) [8.2]
Headache	10 (8.2) [12.9]	7 (5.8) [9.3]	11 (9.2) [15.1]	11 (9.2) [12.9]	41 (8.8) [8.2]
Upper respiratory tract infection	4 (3.3) [5.0]	4 (3.3) [5.2]	5 (4.2) [6.5]	5 (4.2) [5.6]	31 (6.7) [6.1]
Pyrexia	2 (1.6) [2.5]	3 (2.5) [3.8]	4 (3.3) [5.1]	3 (2.5) [3.3]	25 (5.4) [4.8]
Abdominal pain	4 (3.3) [5.1]	3 (2.5) [3.9]	6 (5.0) [7.9]	8 (6.7) [9.2]	24 (5.2) [4.6]
Pharyngitis	1 (0.8) [1.2]	4 (3.3) [5.2]	6 (5.0) [7.7]	2 (1.7) [2.2]	19 (4.1) [3.6]
Herpes simplex	3 (2.5) [3.7]	2 (1.7) [2.6]	2 (1.7) [2.5]	2 (1.7) [2.2]	18 (3.9) [3.4]
Bronchitis	4 (3.3) [5.0]	7 (5.8) [9.1]	1 (0.8) [1.3]	3 (2.5) [3.4]	16 (3.4) [3.0]
Diarrhoea	2 (1.6) [2.5]	1 (0.8) [1.3]	2 (1.7) [2.5]	6 (5.0) [6.8]	15 (3.2) [2.9]

[a] Data cut-off was June 20, 2022; [b] 1 opportunistic infection (herpes zoster) was reported

Laboratory Analyses

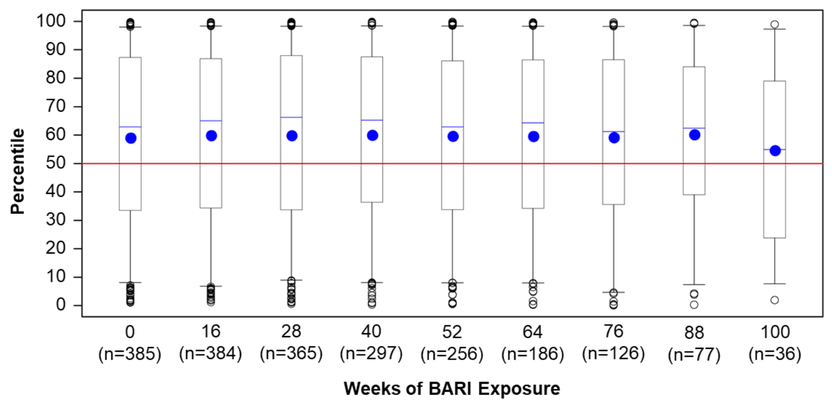
- Categorical shifts to clinically relevant abnormal values for select laboratory analytes (hepatic, CPK, renal, and hematologic) were similar between the placebo and All-BARI groups, except for platelets, total cholesterol, and LDL, where IRs were higher for All-BARI vs. placebo

Analyte	Category	PBO (N=122) n/NAR (%) [IR]	All-BARI Population (N=466) n/NAR (%) [IR]
Platelets	Thrombocytosis (from ≤600 billion cells/L to >600 billion cells/L)	1/122 (0.8) [1.3]	12/461 (2.6) [2.3]
Hemoglobin	Anemia (hemoglobin decrease to <8 g/dL)	0/122	0/462
Neutrophils	Neutropenia (neutrophil decrease to <1000/µL)	3/120 (2.5) [3.8]	8/457 (1.8) [1.5]
Leukocytes	Leukopenia (leukocyte decrease to <2000/µL)	1/122 (0.8) [1.3]	0/461
Lymphocytes	Lymphopenia (lymphocyte decrease to <500/µL)	1/122 (0.8) [1.3]	2/460 (0.4) [0.4]
Cholesterol	Increase to "high" (cholesterol increase to ≥200 mg/dL)	6/104 (5.8) [7.5]	58/397 (14.6) [10.9]
Triglycerides	Increase to "borderline high" or "high"	22/65 (33.8) [27.5]	97/264 (36.7) [18.2]
LDL cholesterol	Increase to "borderline high" or "high" (LDL cholesterol increase to ≥110 mg/dL)	5/93 (5.4) [6.3]	64/363 (17.6) [12.0]
HDL cholesterol	Increase to "acceptable" (HDL cholesterol increase to >45 mg/dL)	10/35 (28.6) [12.5]	68/110 (61.8) [12.7]
Creatinine	Elevated (creatinine increase to >1.5× ULN)	0/122	1/462 (0.2) [0.2][a]
CPK	Any CTCAE grade increase	22/121 (18.2) [27.5]	145/459 (31.6) [27.2]
Serum ALP[b]	Elevated (ALP increase to ≥2× ULN)	2/122 (1.6) [2.5]	5/462 (1.1) [0.9]
Serum AST[b]	Elevated (AST increase to ≥3× ULN)	1/122 (0.8) [1.3]	1/462 (0.2) [0.2]
Serum ALT[b]	Elevated (ALT increase to ≥3× ULN)	2/122 (1.6) [2.5]	1/462 (0.2) [0.2]
Serum total bilirubin[b]	Elevated (serum total bilirubin increase to ≥2× ULN)	1/122 (0.8) [1.3]	7/462 (1.5) [1.3]

[a] 1 BARI-treated patient had elevated creatinine >1.5× ULN (at 1.1 mg/dL [1.6× ULN]), which returned to normal at next test; [b] Data are presented as n/N, where N=number of participants with baseline measurement and that have ≥1 post-baseline measurement

Mean Height Percentile Was Consistent Over Time From Baseline to 100 Weeks (~2 Years)

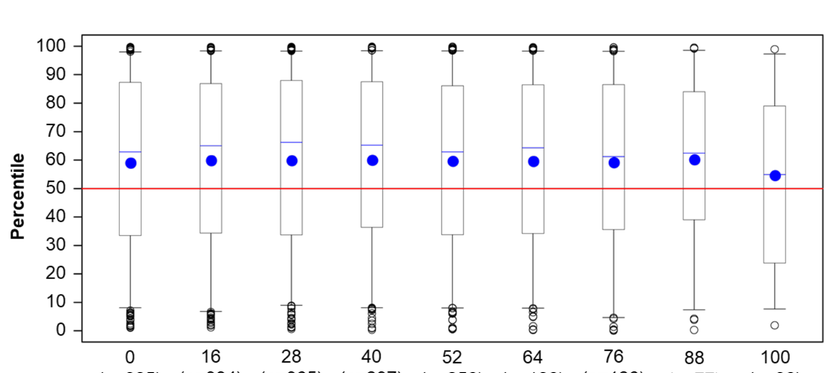
- The distribution of height percentile at baseline (Week 0) in the All-BARI population was consistent with the expected distribution for healthy age- and sex-matched peers (CDC reference), with the mean baseline height at approximately the 50th percentile (blue dot at Week 0) and the majority of patients (box) within the range of 15th to 70th percentile



Note: Red line drawn across the 50th percentile for reference

Mean Weight Percentile Was Consistent Over Time From Baseline to 100 Weeks (~2 Years)

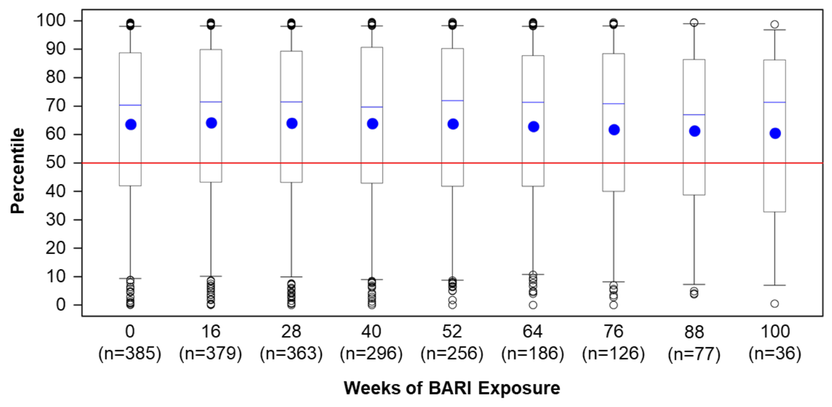
- The distribution of weight percentile at baseline (Week 0) in the All-BARI population was on average higher than the expected distribution for healthy age- and sex-matched peers (CDC reference), with the mean baseline weight at approximately the 60th percentile (blue dot at Week 0)



Note: Red line drawn across the 50th percentile for reference

Mean BMI Percentile Was Consistent Over Time From Baseline to 100 Weeks (~2 Years)

- The distribution of BMI percentile at baseline (Week 0) in the All-BARI population was on average higher than the expected distribution for healthy age- and sex-matched peers (CDC reference), with the mean baseline BMI at approximately the 65th percentile (blue dot at Week 0)



Note: Red line drawn across the 50th percentile for reference

REFERENCES

1. Wollenberg A, et al. *J Eur Acad Dermatol Venereol.* 2021;35:1543-1552.
2. Torrelo A, et al. *Br J Dermatol.* 2023;ljad096.
3. Bieber T, et al. *J Eur Acad Dermatol Venereol.* 2021;35:476-485.

ABBREVIATIONS

AD=atopic dermatitis; AE=adverse event; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BARI=baricitinib; BMI=body mass index; CDC=Centers for Disease Control and Prevention; COVID-19=coronavirus disease 2019; CPK=creatine phosphokinase; CTCAE=Common Terminology Criteria for Adverse Events; HDL=high-density lipoprotein; IR=incidence rate; JAK=Janus kinase; LDL=low-density lipoprotein; LTE=Long-Term Extension; n=number of patients that have ≥1 observation post baseline in the elevated category; NAR=number of patients at risk for the specified abnormality in each treatment group (missing excluded); PBO=placebo; PK=pharmacokinetics; PYE=patient-years of exposure; QD=once daily; SD=standard deviation; TEAE=treatment-emergent AE; ULN=upper limit of normal; W=Week

DISCLOSURES

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