Safety of Baricitinib for the Treatment of Atopic Dermatitis over a Median of 1.6 and up to 3.9 Years Treatment: An Updated Integrated Analysis of 8 Clinical Trials

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BACKGROUND

- Baricitinib is a selective Janus kinase (JAK)1/JAK2 inhibitor approved in Europe, Japan, and multiple other countries for the treatment of moderate-to-severe atopic dermatitis (AD) in adults who are candidates for systemic therapy
- In a previous integrated analysis of safety:
  - The most frequent treatment-emergent adverse events during the 16-week placebo-controlled period were nasopharyngitis, headache, creatine phosphokinase elevations, and diarrhea
  - The number of adverse events of special interest during the long-term follow-up period (median duration, 310 days; maximum duration, 2 years) were small, including the numbers of major adverse cardiovascular events (MACE), venous thromboembolic events, and malignancies

OBJECTIVE

- The purpose of this analysis was to report the safety profile of baricitinib in the adult AD clinical development program with exposure up to 3.9 years

ANALYSIS SETS

PBO-Controlled

- **Weeks 0-16**

Phase 2: JAHG

Phase 3: BREEZE-AD1, BREEZE-AD2, BREEZE-AD4, BREEZE-AD7

- 5-study analysis set
- Phase 2 and 3 AD studies
- PBO, BARI 2-mg, and BARI 4-mg were all options during randomization[a]
- Data derived from these 5 studies for up to 16 weeks of treatment

2-mg and 4-mg Extended

- **Latest data cut-off to December 2021**

Phase 2: JAHG

Phase 3: BREEZE-AD1, BREEZE-AD2, BREEZE-AD4 extended, BREEZE-AD7, BREEZE-AD3 **(LTE)**

- 6-study analysis set
- Phase 2 and 3 AD studies
- BARI 2-mg and BARI 4-mg were both options during randomization or the LTE
- Patients were censored at dose change or followed to the end of study or through data cut-off if no dose change
- Data were analyzed without censoring at rescue

All-BARI-AD

- **Latest data cut-off to December 2021**

Phase 2: JAHG

Phase 3: BREEZE-AD1, BREEZE-AD2, BREEZE-AD4, BREEZE-AD5, BREEZE-AD6, BREEZE-AD7, BREEZE-AD3 **(LTE)**

- All AD studies for which BARI (all available doses) was given to patients, including during the LTE
- All available data without censoring for rescue or dose change

[a] Some studies included BARI 1-mg, which may be approved for patients with renal impairment in some countries

EXPOSURE BY DATASET

- Compared with the previous safety report, an additional 105 patients and 2381 patient-years were added to the All-BARI-AD dataset

	PBO-Controlled[1] (to Week 16)			2-mg and 4-mg Extended (up to 3.9 years)		All-BARI-AD (up to 3.9 years)
	PBO (N=743)	BARI 2-mg (N=576)	BARI 4-mg (N=489)	BARI 2-mg[a] (N=584)	BARI 4-mg (N=497)	All-BARI-AD (N=2636)
Total PY	211.8	169.1	147.1	727.1	800.1	4628.4
Patients with ≥52 weeks of exposure, n (%)	-	-	-	294 (50.3)	315 (63.4)	1659 (62.9)
Patients with ≥84 weeks of exposure, n (%)	-	-	-	159 (27.2)	191 (38.4)	1318 (50.0)
Median duration, days	113.0	113.0	113.0	364.0	475.0	587.5
Maximum exposure, days	168	128	155	1402	1422	1422

Note: All-BARI-AD includes BARI 1-mg, 2-mg, and 4-mg
[a] 103 patients on BARI 2-mg in the originating studies who were non-responders were re-randomized to 4-mg at entry to BREEZE-AD3; their data were censored at the start of the 4-mg dose in the LTE

CONCLUSIONS

- This updated integrated safety analysis in 2636 adult patients with moderate-to-severe AD and up to almost 4 years of exposure showed that baricitinib maintained a similar safety profile as earlier analyses
- There were no increases in the incidence rates of MACE, deep vein thrombosis, pulmonary embolism, malignancies, or serious infections compared with previous analyses
- No new safety signals were identified

BASELINE DEMOGRAPHICS

	PBO-Controlled[1] (to Week 16)			2-mg and 4-mg Extended (up to 3.9 years)		All-BARI-AD (up to 3.9 years)
	PBO (N=743)	BARI 2-mg (N=576)	BARI 4-mg (N=489)	BARI 2-mg (N=584)	BARI 4-mg (N=497)	All-BARI-AD (N=2636)
Age, years	35.7 (13.1)	35.9 (13.5)	35.8 (13.2)	35.9 (13.6)	35.7 (13.1)	36.5 (13.7)
Female, n (%)	298 (40.1)	205 (35.6)	170 (34.8)	205 (35.1)	172 (34.6)	1038 (39.4)
BMI, kg/m^2	25.4 (5.2)	25.8 (5.5)	25.5 (5.1)	25.8 (5.5)	25.5 (5.1)	25.9 (5.4)
Duration of AD, years	24.9 (14.6)	25.0 (14.3)	24.7 (14.8)	24.7 (14.5)	24.3 (15.0)	24.8 (15.0)
Geographic region, n (%)						
Europe	365 (49.1)	297 (51.6)	237 (48.5)	297 (50.9)	237 (47.7)	1130 (42.9)
Japan	134 (18.0)	101 (17.5)	89 (18.2)	101 (17.3)	89 (17.9)	352 (13.4)
Asia (excluding Japan)	99 (13.3)	62 (10.8)	66 (13.5)	70 (12.0)	74 (14.9)	268 (10.2)

Notes: Data reported as mean (SD) unless otherwise indicated. All-BARI-AD includes BARI 1-mg, 2-mg, and 4-mg

BASELINE DISEASE CHARACTERISTICS

	PBO-Controlled[1] (to Week 16)			2-mg and 4-mg Extended (up to 3.9 years)		All-BARI-AD (up to 3.9 years)
	PBO (N=743)	BARI 2-mg (N=576)	BARI 4-mg (N=489)	BARI 2-mg (N=584)	BARI 4-mg (N=497)	All-BARI-AD (N=2636)
Prior topical therapy, n (%)						
Topical corticosteroids	646 (86.9)	496 (86.1)	430 (87.9)	503 (86.1)	438 (88.1)	2352 (89.2)
TCNI	410 (61.6)	316 (65.8)	275 (65.2)	316 (64.9)	277 (64.4)	1333 (55.5)
Prior systemic therapy, n (%)	468 (64.5)	379 (67.1)	287 (60.4)	384 (67.0)	291 (60.2)	1592 (61.3)
Cyclosporine	254 (38.7)	255 (52.8)	172 (41.1)	255 (47.0)	173 (37.8)	812 (32.2)
vIGA-AD™ >3, n (%)	324 (46.7)	257 (47.7)	211 (46.8)	275 (47.1)	224 (45.1)	1206 (45.8)
EASI	31.5 (12.7)	31.3 (13.2)	32.1 (12.9)	30.9 (13.3)	31.3 (13.0)	30.4 (12.8)
SCORAD	67.8 (13.3)	67.9 (13.4)	68.1 (13.2)	67.9 (13.3)	68.0 (13.1)	67.2 (13.3)
BSA involvement, %	51.2 (22.6)	51.2 (23.0)	52.9 (22.5)	50.9 (23.0)	52.6 (22.4)	49.3 (23.0)

Notes: Data reported as mean (SD) unless otherwise indicated. All-BARI-AD includes BARI 1-mg, 2-mg, and 4-mg

ADVERSE EVENTS

- In the adverse event tables, data are presented as follows:

PBO-Controlled	2-mg and 4-mg Extended	All-BARI-AD
n (adjusted %)	n **[adjusted IR]**	n **[IR]**

SUMMARY OF AEs

	PBO-Controlled[1] (to Week 16)			2-mg and 4-mg Extended (up to 3.9 years)		All-BARI-AD (up to 3.9 years)
	PBO (N=743)	BARI 2-mg (N=576)	BARI 4-mg (N=489)	BARI 2-mg (N=584)	BARI 4-mg (N=497)	All-BARI-AD (N=2636)
Total PY of exposure	211.8	169.1	147.1	727.1	800.1	4628.4
Any TEAE	388 (43.2) **[234.7]**	347 (49.3) **[281.4]**	300 (51.0) **[300.1]**	428 **[214.7]**	407 **[216.3]**	2040 **[145.8]**
Serious AEs	21 (2.3) **[8.0]**	10 (1.4) **[4.4]**	14 (2.3) **[7.7]**	33 **[4.2]**	58 **[7.9]**	237 **[5.2]**
Interruption of study drug due to AE	14 (1.6) **[5.4]**	27 (3.4) **[11.6]**	26 (4.6) **[15.8]**	77 **[11.2]**	81 **[11.7]**	410 **[9.6]**
Discontinuation of study drug due to AE	13 (1.4) **[4.6]**	10 (1.5) **[4.7]**	15 (2.1) **[6.5]**	22 **[2.7]**	37 **[4.6]**	158 **[3.4]**
Death	0	0	0	0	0	4 **[0.1]**[a]

Notes: Data are presented as n (adjusted %) [adjusted IR] for the 16-week PBO-Controlled Period, n [adjusted IR] for the BARI 2-mg and 4-mg Extended dataset, and n [IR] for All-BARI-AD.
All-BARI-AD includes BARI 1-mg, 2-mg, and 4-mg
[a] An additional death of unknown cause occurred in a 76-year-old female patient post study completion

MOST COMMON[a] TEAEs IN THE PBO-CONTROLLED DATASETS

	PBO-Controlled[1] (to Week 16)			2-mg and 4-mg Extended (up to 3.9 years)		All-BARI-AD (up to 3.9 years)
	PBO (N=743)	BARI 2-mg (N=576)	BARI 4-mg (N=489)	BARI 2-mg (N=584)	BARI 4-mg (N=497)	All-BARI-AD (N=2636)
Nasopharyngitis	83 (9.5) **[34.9]**	67 (9.5) **[34.1]**	67 (11.3) **[40.8]**	121 **[21.0]**	129 **[22.3]**	530 **[13.8]**
Headache	28 (3.3) **[11.9]**	37 (5.9) **[21.1]**	35 (6.3) **[21.4]**	58 **[8.6]**	55 **[7.4]**	216 **[4.9]**
Blood CPK increased	6 (0.8) **[2.7]**	8 (1.1) **[3.5]**	17 (2.9) **[9.6]**	15 **[2.0]**	27 **[3.3]**	90 **[1.9]**
Diarrhea	15 (1.8) **[6.2]**	10 (1.3) **[4.3]**	15 (2.7) **[9.0]**	18 **[2.3]**	25 **[3.3]**	107 **[2.3]**
Herpes simplex	8 (0.9) **[3.2]**	13 (2.0) **[7.1]**	15 (2.6) **[8.6]**	22 **[3.1]**	36 **[4.9]**	120 **[2.6]**
Upper respiratory tract infection	14 (1.4) **[4.8]**	23 (3.2) **[11.0]**	15 (2.5) **[8.3]**	34 **[5.1]**	45 **[5.8]**	206 **[4.7]**
Upper abdominal pain	10 (1.2) **[4.1]**	10 (1.6) **[5.3]**	14 (2.5) **[8.5]**	18 **[2.4]**	18 **[2.5]**	55 **[1.2]**
Influenza	8 (1.0) **[3.4]**	13 (1.7) **[5.7]**	12 (2.2) **[7.2]**	33 **[4.4]**	30 **[4.7]**	135 **[3.0]**
Oral herpes	9 (1.2) **[4.1]**	10 (1.2) **[4.2]**	12 (2.0) **[6.7]**	21 **[2.9]**	33 **[4.7]**	140 **[3.1]**
Urinary tract infection	8 (0.8) **[2.6]**	9 (1.1) **[3.8]**	11 (2.0) **[6.5]**	17 **[2.4]**	21 **[2.9]**	104 **[2.3]**
Folliculitis	11 (1.2) **[4.0]**	14 (1.8) **[6.2]**	10 (1.5) **[4.9]**	28 **[3.9]**	19 **[2.4]**	109 **[2.4]**
Nausea	8 (0.8) **[2.7]**	14 (1.8) **[5.8]**	4 (0.8) **[2.5]**	18 **[2.3]**	9 **[1.1]**	61 **[1.3]**

Notes: Data are presented as n (adjusted %) [adjusted IR] for the 16-week PBO-Controlled Period, n [adjusted IR] for the BARI 2-mg and 4-mg Extended dataset, and n [IR] for All-BARI-AD
[a] Occurring in ≥2% of patients in any group in the PBO-Controlled dataset

INFECTIONS

	PBO-Controlled[1] (to Week 16)			2-mg and 4-mg Extended (up to 3.9 years)		All-BARI-AD (up to 3.9 years)
	PBO (N=743)	BARI 2-mg (N=576)	BARI 4-mg (N=489)	BARI 2-mg (N=584)	BARI 4-mg (N=497)	All-BARI-AD (N=2636)
Treatment-emergent infections	216 (24.2) **[100.3]**	212 (29.8) **[128.0]**	183 (31.5) **[134.5]**	326 **[99.7]**	312 **[96.0]**	1519 **[67.2]**
Serious infections	5 (0.6) **[2.1]**	3 (0.4) **[1.0]**	3 (0.6) **[1.9]**	12 **[1.4]**	20 **[2.7]**	82 **[1.8]**
Herpes zoster cluster[a]	3 (0.3) **[1.0]**	6 (0.8) **[2.7]**	0	23 **[3.2]**	22 **[3.0]**	127 **[2.8]**
Herpes simplex cluster[b]	22 (2.7) **[9.4]**	25 (3.6) **[12.4]**	35 (6.1) **[21.3]**	52 **[7.5]**	72 **[10.7]**	288 **[6.7]**
Eczema herpeticum[c]	4 (0.4) **[1.3]**	1 (0.2) **[0.7]**	7 (1.4) **[4.5]**	9 **[1.1]**	18 **[2.2]**	67 **[1.4]**
Tuberculosis	0	0	0	0	0	0
Opportunistic infections, excluding tuberculosis	1 (0.1) **[0.4]**	1 (0.1) **[0.3]**	0	5 **[0.6]**	3 **[0.5]**	14 **[0.3]**
Skin infections requiring antibiotic treatment	38 (4.4) **[15.7]**	31 (4.8) **[16.7]**	18 (3.4) **[11.4]**	31 **[4.5]**	19 **[2.5]**	76 **[1.7]**

Notes: Data are presented as n (adjusted %) [adjusted IR] for the 16-week PBO-Controlled Period, n [adjusted IR] for the BARI 2-mg and 4-mg Extended dataset, and n [IR] for All-BARI-AD.
All-BARI-AD includes BARI 1-mg, 2-mg, and 4-mg
[a] Herpes zoster included MedDRA v.24.1 preferred terms of herpes zoster, herpes zoster disseminated, ophthalmic herpes zoster, and varicella zoster virus infection;
[b] Herpes simplex included MedDRA v.24.1 preferred terms of eczema herpeticum, genital herpes and genital herpes simplex, herpes ophthalmic, herpes simplex, ophthalmic herpes simplex, and oral herpes;
[c] Eczema herpeticum group term included eczema herpeticum and Kaposi's varicelliform eruption

TEAEs OF SPECIAL INTEREST

	PBO-Controlled[1] (to Week 16)			2-mg and 4-mg Extended (up to 3.9 years)		All-BARI-AD (up to 3.9 years)
	PBO (N=743)	BARI 2-mg (N=576)	BARI 4-mg (N=489)	BARI 2-mg (N=584)	BARI 4-mg (N=497)	All-BARI-AD (N=2636)
CV TEAEs of special interest						
MACE	0	0	0	1 **[0.10]**	1 **[0.11]**	7 **[0.15]**
DVT/PE	0	0	1 (0.1) **[0.38]**	0	2 **[0.23]**	3 **[0.06]**
DVT	0	0	0	0	0	0
PE	0	0	1 (0.1) **[0.38]**	0	2 **[0.23]**	3 **[0.06]**
Malignancies						
Excluding NMSC	2 (0.2) **[0.66]**	0	0	2 **[0.28]**	0	14 **[0.30]**
NMSC	1 (0.2) **[0.68]**	0	0	1 **[0.10]**	1 **[0.12]**	11 **[0.23]**
GI disorders						
GI perforations	0	0	0	0	1 **[0.17]**	1 **[0.02]**
Ocular AEs						
Conjunctival disorders	15 (2.1) **[7.5]**	12 (1.6) **[5.6]**	6 (1.2) **[3.7]**	26 **[3.6]**	26 **[3.7]**	144 **[3.2]**

Notes: Data are presented as n (adjusted %) [adjusted IR] for the 16-week PBO-Controlled Period, n [adjusted IR] for the BARI 2-mg and 4-mg Extended dataset, and n [IR] for All-BARI-AD.
All-BARI-AD includes BARI 1-mg, 2-mg, and 4-mg

REFERENCE

1. Bieber T, et al. *J Eur Acad Dermatol Venereol*. 2021;35:476-485.

ABBREVIATIONS

AD=atopic dermatitis; AE=adverse event; BARI=baricitinib; BMI=body mass index; BSA=body surface area; CPK=creatinine phosphokinase; CV=cardiovascular; DVT=deep vein thrombosis; EASI=Eczema Area and Severity Index; GI=gastrointestinal; IR=incidence rate; LTE=Long-Term Extension; MACE=major adverse cardiovascular event; NMSC=non-melanoma skin cancer; PBO=placebo; PE=pulmonary embolism; PY=patient-years; SCORAD=SCORing Atopic Dermatitis; SD=standard deviation; TCNI=topical calcineurin inhibitor; TEAE=treatment-emergent AE

DISCLOSURES

- **T. Bieber** was a speaker, consultant, and/or Investigator for: AbbVie, Affibody, Almirall, AnaptysBio, Arena Pharmaceuticals, Asana BioSciences, ASLAN Pharmaceuticals, Bayer Pharmaceuticals, BioVersys, Boehringer Ingelheim, Bristol Myers Squibb, Connect Biopharma, Dermavant, Domain Therapeutics, Eli Lilly and Company, EQRx, Galderma, GlaxoSmithKline, Glenmark Pharmaceuticals, Incyte Corporation, Innovaderm Research, IQVIA, Janssen, Kymab, Kyowa Kirin, L'Oréal, LEO Pharma, LG Chem, Merck Sharp & Dohme, Novartis, Numab, OM Pharma, Pfizer, Pierre Fabre, Q32 Bio, RAPT Therapeutics, Sanofi/Regeneron, and UCB Pharma; and is Founder and Chairman of the Board of the non-profit biotech: Davos Biosciences; **N. Katoh** has received grants and/or personal fees from: A2 Healthcare, AbbVie, Boehringer Ingelheim Japan, Celgene Japan, Eisai, Eli Lilly Japan, Kyowa Kirin, LEO Pharma, Maruho, Mitsubishi Tanabe Pharma, Janssen, Sanofi, Sun Pharma, Taiho Pharmaceutical, and Torii Pharmaceutical, outside the submitted work; **E. L. Simpson** has received grants from or serves as Principal Investigator for: AbbVie, Amgen, Arcutis, ASLAN Pharmaceuticals, Castle Biosciences, CorEvitas, Dermavant, Dermira, Eli Lilly and Company, Incyte Corporation, Kymab, Kyowa Hakko Kirin, LEO Pharma, Pfizer, Regeneron, Sanofi, and Target RWE; and has received personal fees from: AbbVie, Amgen, Arena Pharmaceuticals, ASLAN Pharmaceuticals, Boston Consulting Group, Collective Acumen, Dermira, Eli Lilly and Company, Evidera, Excerpta Medica, Forte Biosciences, Galderma, GlaxoSmithKline, Incyte Corporation, Janssen, Kyowa Kirin, LEO Pharma, Medscape, Merck, Pfizer, Physicians World, Regeneron, Roivant Sciences, Sanofi Genzyme, Trevi Therapeutics, Valeant Pharmaceuticals, and WebMD; **M. De Bruin-Weller** has served as consultant, speaker, advisor, and/or advisory board member for: AbbVie, Almirall, Arena Pharmaceuticals, ASLAN Pharmaceuticals, Eli Lilly and Company, Galderma, Janssen, LEO Pharma, Pfizer, Regeneron, and Sanofi Genzyme; **D. Thaçi** has received personal fees from: AbbVie, Almirall, Amgen, Asana BioSciences, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly and Company, Janssen Cilag, Kyowa Kirin, LEO Pharma, Novartis, Pfizer, Regeneron, Sandoz, Sanofi-Aventis, and UCB Pharma; and has received grants from: AbbVie, LEO Pharma, and Novartis; **A. Torrelo** has been a consultant and/or Principal Investigator for: AbbVie, Eli Lilly and Company, Novartis, Pfizer, Pierre Fabre, and Sanofi; **A. Sontag**, **S. Grond**, **M. Issa, T. Cardillo**, and **K. Holzwarth** are employees and shareholders of: Eli Lilly and Company; **X. Lu** reports no conflicts of interest; **J. P. Thyssen** has been a consultant for and/or has received grant, research, and/or honorarium support from: AbbVie, Eli Lilly and Company, LEO Pharma, Pfizer, Regeneron, and Sanofi Genzyme; **L. Ghys** (Non-Author Presenter) is an employee and minor shareholder of Eli Lilly and Company
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