SUPPLEMENTARY FILE

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Article title: Extended safety analysis of baricitinib 2 mg in adult patients with atopic dermatitis: an integrated analysis from 8 randomized clinical trials

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Supplementary Methods

Key inclusion criteria

1. Are at least 18 years of age
2. Have moderate to severe atopic dermatitis (AD), defined as:
    a. Eczema Area and Severity Index score of ≥16 (≥12 for the phase 2 study)
    b. Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD™) score of ≥3 (not used in the phase 2 study)
    c. ≥10% body surface area involvement at baseline
3. Have a documented history of inadequate response to topical therapies and, in BREEZE-AD4, an inadequate response to cyclosporine.

Key exclusion criteria

Patients were excluded from study enrollment if they met any of the following criteria:

1. Currently experiencing or have a history of other concomitant skin conditions that could affect assessment of AD lesions.
2. A history of eczema herpeticum (EH) within 12 months prior to screening or ≥2 episodes of EH in the past.
3. Have experienced a venous thromboembolism (VTE) or major adverse cardiovascular event (MACE) within 12 weeks of screening or are at high risk of VTE, the definition of which varied by study:
    a. For BREEZE-AD1, BREEZE-AD2, BREEZE-AD4, and BREEZE-AD7: have a history of recurrent (≥2) VTE or are considered at high risk of VTE as deemed by the investigator.
    b. For BREEZE-AD5: have a history of VTE, or are considered at high risk for VTE as deemed by the investigator, or have 2 or more of the following risk factors for VTE:
        i. Aged >65 years
        ii. BMI >35 kg/m^2
        iii. Oral contraceptive use and current smoker
    c. For BREEZE-AD6: have a history of VTE or are considered at high risk of VTE as deemed by the investigator.

Description for adjudication

All adverse events (AEs) suggestive of a possible MACE, DVT, pulmonary embolisms (PE), or other peripheral venous thrombosis were adjudicated in a blinded manner by an experienced external independent clinical event committee. Adjudication determined whether these AEs qualified as MACE, DVT, PE, or other peripheral venous thrombosis based on evaluation of case descriptions and any diagnostic tests available. AEs meeting the adjudication committee definitions for these specific events were considered positively adjudicated. A positively adjudicated event provides additional diagnostic confirmation but does not assess causal relationship to the study drug. Further details are provided in Table S2.

Supplementary Results

Selected laboratory analytes over time

Hematology

Mean platelet counts increased with baricitinib 2 mg at Weeks 4–16 and remained increased through 68 weeks of treatment. Mean hemoglobin and neutrophil counts decreased with baricitinib 2 mg at Week 4 and stabilized slightly below baseline over time. Mean lymphocyte counts increased with baricitinib 2 mg at Week 4 and returned to baseline over time (Figure S1).

Cholesterol

Mean low-density lipoproteins (LDL) and high-density lipoproteins (HDL) were elevated with baricitinib 2 mg at Week 24 and Week 12, respectively, and remained elevated through 68 weeks of treatment (Figure S1).

Hepatic

Mean alanine aminotransferase (ALT) remained largely stable throughout the treatment period with baricitinib 2 mg (Figure S1).

Table S1 Summary of patient populations included in the integrated analysis

Study	Treatments[a]	Dataset	Baricitinib therapy	Treatment period (weeks)	Data cutoff
PHASE 2					
I4V-MC-JAHG (NCT02576938)	Placebo (*N*=49) Bari 2 mg (*N*=37)	Placebo-controlled All-bari-2-mg-AD	In combination with TCS	16	14 March 2017
PHASE 3					
BREEZE-AD1 (NCT03334396)	Placebo (*N*=249) Bari 2 mg (*N*=123)	Placebo-controlled All-bari-2-mg-AD	Monotherapy (rescue with TCS permitted[b])	16	17 January 2019
BREEZE-AD2 (NCT03334422)	Placebo (*N*=244) Bari 2 mg (*N*=123)	Placebo-controlled All-bari-2-mg-AD	Monotherapy (rescue with TCS permitted[b])	16	24 January 2019
BREEZE-AD7 (NCT03733301)	Placebo (*N*=109) Bari 2 mg (*N*=109)	Placebo-controlled All-bari-2-mg-AD	In combination with TCS	16	29 August 2019
BREEZE-AD4 (NCT03428100)	Placebo (*N*=93) Bari 2 mg (*N*=185)	Placebo-controlled All-bari-2-mg-AD	In combination with TCS	16 weeks for placebo-controlled; study is ongoing (>74 weeks for this analysis)	24 April 2020
BREEZE-AD5 (NCT03435081)	Placebo (*N*=147)	Placebo-controlled	Monotherapy (weeks 0 to 16)	16 weeks for placebo-controlled; study is	24 April 2020

	Bari 2 mg (*N*=146)	All-bari-2-mg-AD	In combination with TCS (weeks 16 to 104	ongoing (>89 weeks for this analysis)	
LTE					
BREEZE-AD3[c] (NCT03334435)	Placebo (*N*=86) Bari 2 mg (*N*=512) Open-label addendum: Bari 2 mg (*N*=247)	All-bari-2-mg-AD	In combination with TCS	200 weeks; study is ongoing (>108 cumulative weeks for this analysis that includes patients from originating studies BREEZE-AD1, AD2, AD7)	24 April 2020
BREEZE-AD6[d] (NCT03559270)	Bari 2 mg (*N*=322)	All-bari-2-mg-AD	In combination with TCS	104 weeks; study is ongoing (>89 cumulative weeks for this analysis that includes patients from BREEZE-AD5)	24 April 2020

AD atopic dermatitis, *Bari* baricitinib, *LTE* long-term extension, *TCS* topical corticosteroids

[a]Treatment arms depicted in table are representative of those included in this analysis and may not include all treatment arms included in the studies

[b]Investigators were required to attempt to manage patients with emollients; however, patients who experienced unacceptable or worsening symptoms of AD could be rescued at any time at the discretion of the investigator

[c]Patients from studies BREEZE-AD1, BREEZE-AD2, and BREEZE-AD7 were eligible to enroll in BREEZE-AD3

[d]Patients from study BREEZE-AD5 were eligible to enroll in BREEZE-AD6

Table S2 Safety outcome definition and assessments

Safety Outcome	Definition/Assessment
Treatment-emergent adverse events[a]	
TEAE	An event that first occurred or worsened in severity after the first dose of study treatment, and on or prior to the last visit date during the analysis period (treatment period plus up to 30 days off-drug follow-up time)
SAE	Any event meeting ICH E2A seriousness criteria
TEAE leading to temporary interruption of study drug	When study drug was temporarily interrupted because of an adverse event, either as defined in the study protocol or as determined by the investigator, and study drug was restarted per protocol or at the discretion of the investigator
TEAE leading to permanent discontinuation of study drug	When study drug was permanently discontinued because of an adverse event either as defined in the study protocol as or determined by the investigator
Adverse events of special interest[b]	
Infections	
Serious infections	All infections that met the ICH SAE criteria
Herpes zoster	Events were reported using the preferred term of herpes zoster
Herpes simplex	The cluster for herpes simplex included preferred terms of herpes simplex, oral herpes, Kaposi's varicelliform eruption, eczema herpeticum, ophthalmic herpes simplex, genital herpes, and genital herpes simplex. All cases of herpes simplex were assessed for skin condition at the time of infection using the vIGA-AD
Eczema herpeticum	The cluster for eczema herpeticum included the preferred terms of eczema herpeticum and Kaposi's varicelliform eruption
Tuberculosis	Cases of tuberculosis were classified separately from opportunistic infections (OIs)
Opportunistic infections	Potential OIs were identified using a list of MedDRA preferred terms, created to align with the consensus recommendations for reporting OIs in clinical trials and post marketing surveillance of drugs used to treat immune-mediated inflammatory diseases[1]. Modifications to this approach were: • Candidiasis infections involving only the oral cavity and pharynx were not considered as OIs; to meet criteria for classification as OI, diagnostic evidence must confirm infection of the esophagus or below

Safety Outcome	Definition/Assessment
	• Localized herpes zoster infections were not considered OIs; only multidermatomal (>3 dermatomes) and/or disseminated infections were considered OIs. A second event of herpes zoster was adjudicated to be an OI if it was a second discrete herpes zoster infection in a different location • Treatment-emergent, active tuberculosis infections were summarized separately from OIs The cases of potential OIs were medically reviewed internally by 2 blinded medical physicians and/or clinical research scientists, completing separate reviews, to determine whether they met the definition of and were classified as OIs
Malignancy	Malignancies were identified using terms from the malignant tumors SMQ (SMQ 20000194). NMSCs and malignancies excluding NMSCs were reported separately. All cases identified by the malignant tumors SMQ were assessed through medical review to determine confirmed NMSC cases
NMSC	Cases of NMSC were defined by the terms: • Squamous cell carcinoma of skin • Bowen's disease • Basal cell carcinoma • Basosquamous carcinoma • Basosquamous carcinoma of skin • Squamous cell carcinoma • Skin squamous cell carcinoma metastatic • Skin cancer • Carcinoma in situ of skin • Keratoacanthoma • Vulvar squamous cell hyperplasia • Skin squamous cell carcinoma recurrent
MACE	Events were identified by the investigative site or through medical review and were sent to a blinded external Clinical Event Committee for adjudication. Positively adjudicated cardiovascular events categorized as MACE included: • Cardiovascular death • Mycoardial infarction • Stroke
DVT and/or PE	Events were identified by the investigative site or through medical review and were sent to a blinded external Clinical Event Committee for adjudication. This committee categorized events as: • DVT (above the knee) • PE • or other peripheral venous thrombosis

Safety Outcome	Definition/Assessment
Gastrointestinal perforation	TEAEs related to potential GI perforations were analyzed using reported AEs. Identification of these events was based on review of the preferred terms of the MedDRA SMQ 20000107, GI perforations. Potential GI perforations identified by the SMQ search were provided as a listing for internal review by the medical safety team. Each case was assessed to determine whether it represented a GI perforation
Conjunctival disorders	The cluster for conjunctival disorders was included based on findings with dupilumab[2], a recently approved biologic medication for the treatment of AD Preferred terms that were included in the analysis of conjunctival disorders included: • Conjunctivitis • Conjunctivitis allergic • Keratitis • Non-infective conjunctivitis • Conjunctival hemorrhage • Conjunctival hyperemia • Dry eye • Giant papillary conjunctivitis • Seasonal allergy The search for these terms was based on the MedDRA SMQ 20000175
Laboratory Analysis	
	Clinical laboratory tests including hematology and chemistry, including lipids, were performed at scheduled visits and assessed for each dataset. Evaluation of laboratory analytes included shift summaries in terms of CTCAE and NCEP for laboratory lipid analytes. Changes from baseline in laboratory analytes, to each scheduled visit time point were also evaluated.

AD atopic dermatitis, *AE* adverse event, *CTCAE* Common Terminology Criteria for Adverse Events, *DVT* deep vein thrombosis, *GI* gastrointestinal, *ICH* International Conference on Harmonisation, *MACE* major adverse cardiovascular event, *MedDRA* Medical Dictionary for Regulatory Activities, *NCEP* National Cholesterol Education Program, *NMSC* nonmelanoma skin cancer, *OI* opportunistic infection, *PE* pulmonary embolism, *PT* preferred term, *SAE* serious adverse event, *SMQ* standardized MedDRA queries, *TEAE* treatment-emergent adverse event, *vIGA-AD* validated Investigator Global Assessment for Atopic Dermatitis, *VTE* venous thromboembolism
Table was adapted from Bieber *et al.* 2021[3]

[a]Adverse events were classified based on the Medical Dictionary for Regulatory Activities (MedDRA), version 23.0
[b]Clusters were informed by the combination of standardized MedDRA queries (SMQs), medical assessment of preferred terms, and clusters previously used to establish the safety profile of baricitinib in rheumatoid arthritis

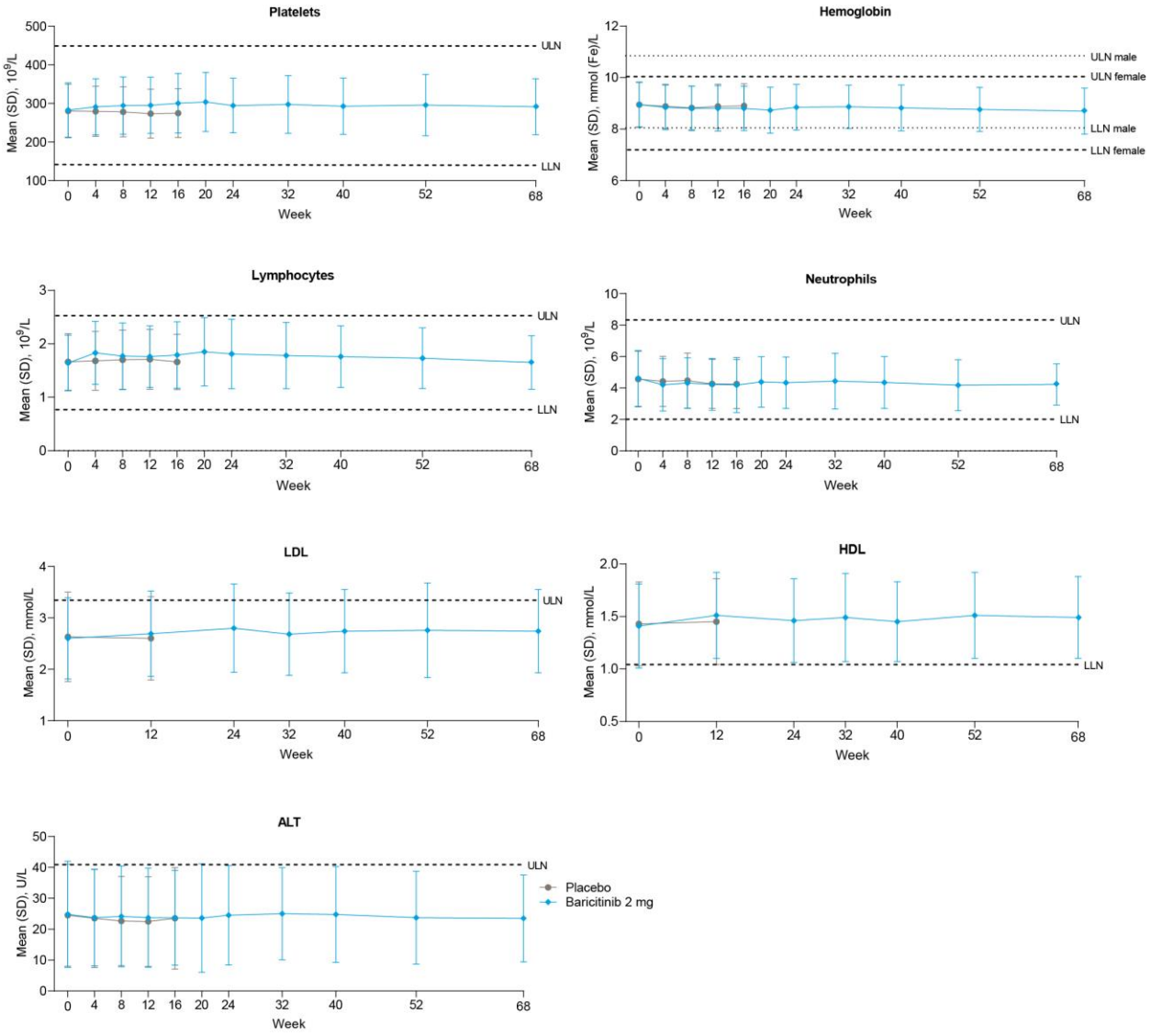
Table S3 Conjunctival disorders by preferred term within cluster

	Placebo-controlled (to Week 16)[a]		**All-bari-2-mg-AD**
	Placebo (*N*=889) n (adj %) [adj IR]	Baricitinib 2 mg (*N*=721) n (adj %) [adj IR]	All-bari-2-mg-AD (*N*=1598) n [IR]
Conjunctival disorders	18 (2.4) [8.7]	15 (2.0) [6.8]	51 [3.5]
Conjunctivitis	2 (0.3) [1.0]	7 (0.9) [3.1]	25 [1.7]
Conjunctivitis allergic	8 (1.0) [3.6]	4 (0.6) [2.0]	14 [1.0]
Seasonal allergy	2 (0.2) [0.7]	3 (0.3) [1.2]	5 [0.3]
Conjunctival hyperaemia	0	1 (0.1) [0.4]	1 [0.1]
Conjunctival haemorrhage	2 (0.3) [1.1]	0	2 [0.1]
Giant papillary conjunctivitis	1 (0.1) [0.3]	0	0
Dry eye	4 (0.7) [2.5]	0	1 [0.1]
Keratitis	0	0	1 [0.1]
Xerophthalmia	0	0	1 [0.1]
Conjunctival irritation	0	0	1 [0.1]

AD atopic dermatitis, *Adj* adjusted, *IR* incidence rate, *N* number of patients in the safety population, *n* number of patients in the specified category

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

Fig. S1 Selected laboratory analytes over time[a]



ALT alanine aminotransferase, *Fe* iron, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *LLN* lower limit of normal, *SD* standard deviation, *U* units, *ULN* upper limit of normal

[a]Baricitinib 2 mg data beyond the 16-week placebo-controlled period are included from an extended dataset including studies BREEZE-AD1, BREEZE-AD2, BREEZE-AD3, BREEZE-AD4, BREEZE-AD5, and BREEZE-AD6

References

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