Efficacy and Safety of Baricitinib in Moderate-to-Severe Atopic Dermatitis: Results of Two Phase 3 Monotherapy Randomized, Double-Blind, Placebo-Controlled 16-Week Trials (BREEZE-AD1 and BREEZE-AD2)

P01

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BACKGROUND

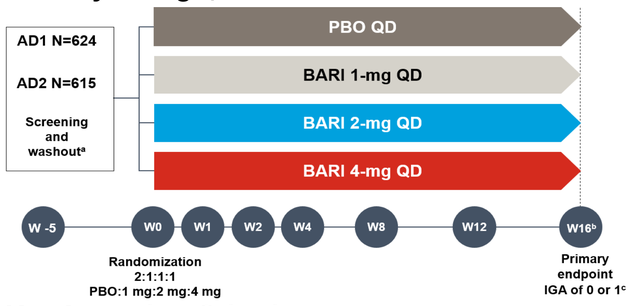
- Atopic dermatitis (AD) is a common inflammatory and pruritic skin disease characterized by complex cytokine signaling involving cross-talk between keratinocytes, neurons, immune cells, and inflammatory mediators
- BREEZE-AD1 (NCT03334396) and BREEZE-AD2 (NCT03334422) are the first of 7 Phase 3 studies of baricitinib, a selective Janus kinase (JAK)1 and JAK2 inhibitor, in moderate-to-severe AD

OBJECTIVE

- To assess the efficacy and safety of baricitinib in adults with moderate-to-severe AD

METHODS

Study Design, BREEZE-AD1 and BREEZE-AD2



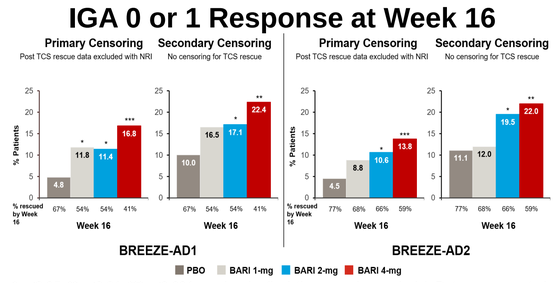
[a]All patients washed out of AD treatments; [b]Patients who did not enroll into BREEZE-AD3 completed a post-treatment follow-up period (28 days); [c]Proportion of participants achieving IGA of 0 or 1 with a ≥2-point improvement
AD=atopic dermatitis; BARI=baricitinib; BSA=body surface area; EASI=Eczema Area Severity Index; IGA=Investigator's Global Assessment; LTE=long-term extension; PBO=placebo; QD=once daily; TCS=topical corticosteroid; W=week

Key Inclusion Criteria

- ≥18-years-old, and diagnosis of AD for ≥12 months
- Moderate-to-severe AD at Screening and Randomization, defined as:
  - IGA 3 or 4
  - EASI ≥16
  - BSA ≥10%
- Inadequate response or intolerance to ≥1 topical medication <6 months prior to screening
- 2-week washout for TCS and 4-week washout for systemic therapies
- No TCS use allowed during treatment period, except as rescue

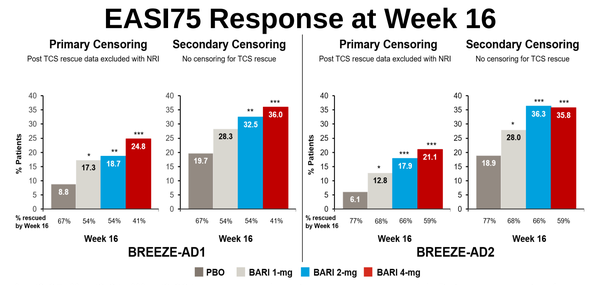
KEY RESULTS

IGA 0 or 1 Response at Week 16



* p≤0.05; ** p≤0.01; *** p≤0.001 vs. placebo (logistic regression analysis); Data are presented for the ITT Population; Patients were allowed TCS rescue from Day 1; BARI=baricitinib; IGA=Investigator's Global Assessment; ITT=Intent to treat; NRI=non-responder imputation; PBO=placebo; TCS=topical corticosteroid

EASI75 Response at Week 16



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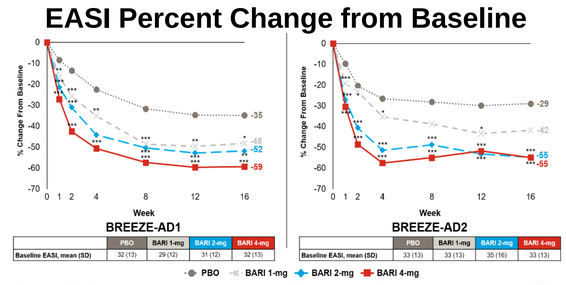
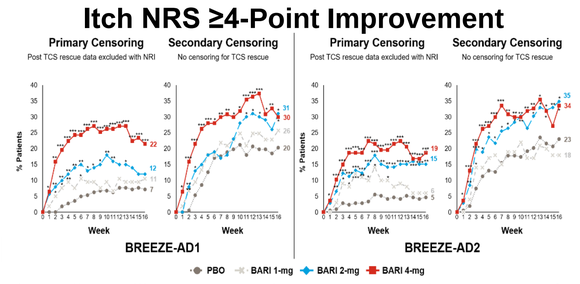
EASI Percent Change from Baseline



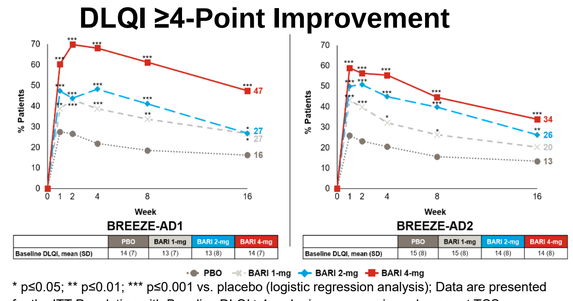
* p≤0.05; ** p≤0.01; *** p≤0.001 vs. placebo (MMRM analysis); Data are presented for the ITT Population with primary censoring, where post TCS rescue data were excluded with MMRM
BARI=baricitinib; EASI=Eczema Area Severity Index; ITT=Intent to treat; MMRM=mixed-model repeated measures; PBO=placebo; SD=standard deviation; TCS=topical corticosteroid

Itch NRS ≥4-Point Improvement



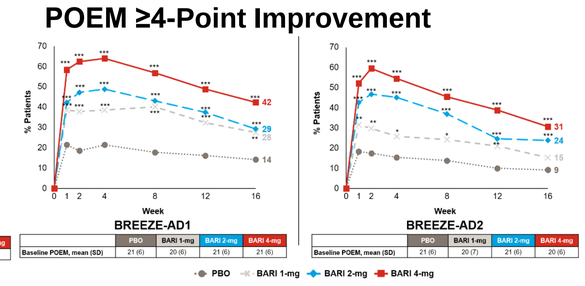
* p≤0.05; ** p≤0.01; *** p≤0.001 vs. placebo (logistic regression analysis); Data are presented for the ITT Population with Baseline Itch NRS ≥4; Patients were allowed TCS rescue from Day 1; BARI=baricitinib; ITT=Intent to treat; NRI=non-responder imputation; PBO=placebo; SD=standard deviation; TCS=topical corticosteroid

DLQI ≥4-Point Improvement



* p≤0.05; ** p≤0.01; *** p≤0.001 vs. placebo (logistic regression analysis); Data are presented for the ITT Population with Baseline DLQI ≥4 and primary censoring, where post TCS rescue data were excluded with NRI
BARI=baricitinib; DLQI=Dermatology Life Quality Index; ITT=Intent to treat; PBO=placebo; SD=standard deviation; TCS=topical corticosteroid

POEM ≥4-Point Improvement



* p≤0.05; ** p≤0.01; *** p≤0.001 vs. placebo (logistic regression analysis); Data are presented for the ITT Population with Baseline POEM ≥4 and primary censoring, where post TCS rescue data were excluded with NRI
BARI=baricitinib; ITT=Intent to treat; PBO=placebo; POEM=Patient Oriented Eczema Measure; SD=standard deviation; TCS=topical corticosteroid

Baseline Characteristics and Disease Activity

	BREEZE-AD1				BREEZE-AD2			
	PBO (N=249)	BARI 1-mg (N=127)	BARI 2-mg (N=123)	BARI 4-mg (N=125)	PBO (N=244)	BARI 1-mg (N=125)	BARI 2-mg (N=123)	BARI 4-mg (N=123)
Age, years	35 (13)	36 (12)	35 (14)	37 (13)	35 (13)	33 (10)	36 (13)	34 (14)
Female, %	41%	39%	33%	34%	37%	36%	47%	33%
Race								
Caucasian, %	60%	58%	61%	56%	69%	68%	69%	67%
Asian, %	30%	31%	28%	33%	30%	29%	30%	31%
IGA of 4, %	42%	42%	42%	41%	50%	51%	50%	51%
EASI	32 (13)	29 (12)	31 (12)	32 (13)	33 (13)	33 (13)	35 (16)	33 (13)
Itch NRS	6.7 (2.0)	6.1 (2.1)	6.4 (2.2)	6.5 (2.0)	6.8 (2.2)	6.4 (2.2)	6.6 (2.2)	6.6 (2.2)
DLQI	14 (7)	13 (7)	13 (8)	14 (7)	15 (8)	15 (8)	14 (8)	14 (8)
POEM	21 (6)	20 (6)	21 (6)	21 (6)	21 (6)	20 (7)	21 (6)	20 (6)

Data are mean (standard deviation) unless stated otherwise
BARI=baricitinib; EASI=Eczema Area Severity Index; DLQI=Dermatology Life Quality Index; IGA=Investigator's Global Assessment; NRS=Numeric Rating Scale; PBO=placebo; POEM=Patient Oriented Eczema Measure

Overview of Adverse Events

	BREEZE-AD1/-AD2 Pooled Data			
	PBO (N=493)	BARI 1-mg (N=251)	BARI 2-mg (N=246)	BARI 4-mg (N=248)
Any TEAE	272 (55)	135 (54)	142 (58)	139 (56)
TEAE by maximum severity				
Mild	158 (32)	73 (29)	88 (36)	92 (37)
Moderate	98 (20)	51 (20)	46 (19)	42 (17)
Severe	16 (3)	11 (4)	8 (3)	5 (2)
Serious adverse events	15 (3)	10 (4)	3 (1)	3 (1)
Death	0	0	0	0
AEs leading to study discontinuation	2 (0)	3 (1)	3 (1)	2 (1)

Data are presented as n (%); AD=atopic dermatitis; AE=adverse event; BARI=baricitinib; PBO=placebo; TEAE=treatment-emergent adverse event

Most Frequent TEAEs, Preferred Terms with ≥2% Occurrence in the Baricitinib 4-mg Group

	BREEZE-AD1/-AD2 Pooled Data			
	PBO (N=493)	BARI 1-mg (N=251)	BARI 2-mg (N=246)	BARI 4-mg (N=248)
Nasopharyngitis	56 (11.4)	35 (13.9)	28 (11.4)	22 (8.9)
Headache	21 (4.3)	13 (5.2)	23 (9.3)	21 (8.5)
Blood creatine phosphokinase increased	3 (0.6)	5 (2.0)	2 (0.8)	11 (4.4)
Upper respiratory tract infection	11 (2.2)	7 (2.8)	8 (3.3)	8 (3.2)
Abdominal pain upper	8 (1.6)	4 (1.6)	6 (2.4)	7 (2.8)
Diarrhea	11 (2.2)	11 (4.4)	3 (1.2)	7 (2.8)
Herpes simplex[a]	4 (0.8)	5 (2.0)	8 (3.3)	7 (2.8)
Urinary tract infection	7 (1.4)	1 (0.4)	2 (0.8)	6 (2.4)
Cough	5 (1.0)	1 (0.4)	2 (0.8)	5 (2.0)

[a]Includes events of Herpes simplex by preferred term. Data are presented as n (%)
BARI=baricitinib; PBO=placebo; TEAE=treatment-emergent adverse event

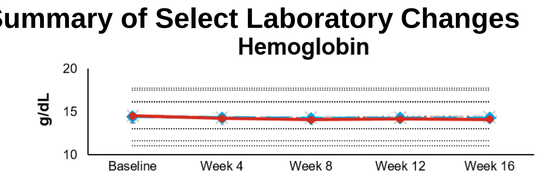
Treatment-Emergent Adverse Events of Special Interest (Blinded for Patients Not Discontinued from the Study)

	BREEZE-AD1/-AD2 Pooled Data			
	PBO (N=493)	BARI 1-mg (N=251)	BARI 2-mg (N=246)	BARI 4-mg (N=248)
Deaths	0	0	0	0
Deep vein thrombosis	0	0	0	0
Pulmonary embolism	0	0	0	0
Positively Adjudicated MACE	0	0	0	0
GI perforations	0	0	0	0
Malignancies other than NMSC[a]	2 (0.4%)	0	0	0
Breast cancer	*1 (0.2%)*	*0*	*0*	*0*
Papillary thyroid cancer	*1 (0.2%)*	*0*	*0*	*0*
NMSC[b]	-	-	-	-
Bowen's disease	*1 case*			
Keratoacanthoma	*1 case*			

[a]Malignancy cases have been discontinued from the study, and unblinded after trial completion; [b]NMSC cases are not yet unblinded to investigators and treatment groups cannot be reported. Data are presented as n (%)
BARI=baricitinib; GI=gastrointestinal; MACE=major adverse cardiovascular events; NMSC=non melanoma skin cancer; PBO=placebo

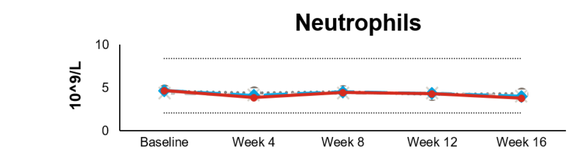
Summary of Select Laboratory Changes

Hemoglobin



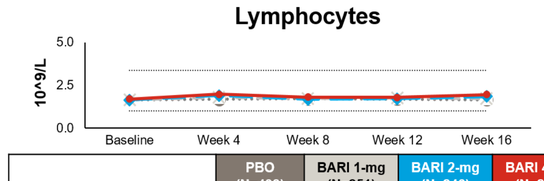
	PBO (N=493) n/NAR (%)	BARI 1-mg (N=251) n/NAR (%)	BARI 2-mg (N=246) n/NAR (%)	BARI 4-mg (N=248) n/NAR (%)
Hemoglobin CTCAE Grade 3+ (<8.0 g/dL)	0	0	0	0

Neutrophils



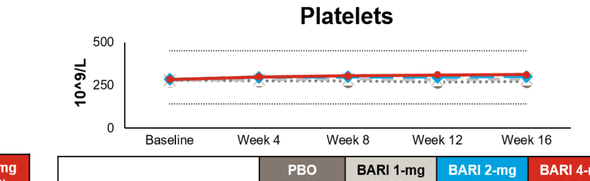
	PBO (N=493) n/NAR (%)	BARI 1-mg (N=251) n/NAR (%)	BARI 2-mg (N=246) n/NAR (%)	BARI 4-mg (N=248) n/NAR (%)
Neutrophils CTCAE Grade 3+ (<1000/mm³)	0	0	0	0

Lymphocytes



	PBO (N=493) n/NAR (%)	BARI 1-mg (N=251) n/NAR (%)	BARI 2-mg (N=246) n/NAR (%)	BARI 4-mg (N=248) n/NAR (%)
Lymphocytes CTCAE Grade 3+ (<500/mm³)	0	1 (0.4%)	0	0

Platelets



	PBO (N=493) n/NAR (%)	BARI 1-mg (N=251) n/NAR (%)	BARI 2-mg (N=246) n/NAR (%)	BARI 4-mg (N=248) n/NAR (%)
Platelets >600x10⁹/L	0	2 (0.8%)	4 (1.6%)	1 (0.4%)

PBO BARI 1-mg BARI 2-mg BARI 4-mg

Laboratory data presented from combined BREEZE-AD1 and BREEZE-AD2 results
BARI=baricitinib; CTCAE=Common Terminology Criteria for Adverse Events; NAR=number of patients at risk for the specified abnormality in each treatment group (missing excluded); PBO=placebo

CONCLUSIONS

- Both studies met the primary endpoint, with significantly more patients achieving an IGA 0 or 1 on baricitinib 4-mg and 2-mg compared to placebo
- Baricitinib 4-mg showed statistical significance for every key secondary endpoint tested in both studies
- Baricitinib showed rapid onset of action, improving skin inflammation (EASI75) and patient-reported outcome measures (Itch NRS, POEM, and DLQI) as early as Week 1
  - Data not shown, but there were also significant improvements in Skin Pain NRS and ADSS
- The safety profile remained consistent with prior findings, with no new or unexpected safety concerns
- There were no deaths, VTEs, MACE, or GI perforations during the 16-week placebo-controlled period
- Treatment with baricitinib improved the signs and symptoms of moderate-to-severe AD compared to placebo, and may represent a novel oral treatment option for patients with moderate-to-severe AD

AD=atopic dermatitis; ADSS=Atopic Dermatitis Sleep Scale; DLQI=Dermatology Life Quality Index; EASI=Eczema Area Severity Index; GI=gastrointestinal; IGA=Investigator's Global Assessment; MACE=major adverse cardiovascular events; NRS=Numeric Rating Scale; POEM=Patient Oriented Eczema Measure; VTEs=venous thromboembolisms

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Disclosures

- **E. L. Simpson** has received has been an investigator for: Eli Lilly and Company, Galderma, Leo Pharma, Merck, Pfizer, Regeneron, and a consultant with honorarium for: AbbVie, Boehringer Ingelheim, Dermavant, Eli Lilly and Company, Incyte, Leo Pharma, Pfizer, Pierre Fabre Dermo Cosmetique, Regeneron, and Sanofi Genzyme; **J-P Lacour** has received grants/research support as an investigator and honoraria, advisory board, or consulting fees from: AbbVie, BMS, Boehringer Ingelheim, Celgene, Dermira, Galderma, Janssen, Eli Lilly and Company, Merck, Novartis, Regeneron, Roche, and Sanofi; **L. Spelman** has received grants as an investigator and honoraria or consulting fees from: AbbVie, Amgen, Ascend Biopharma, Australian Wool Innovation, BMS, Celgene, Dermira, Eli Lilly and Company, Galderma, Genentech, GSK, Janssen, Leo Pharma, Merck, Novartis, Phosphagenics, Regeneron, Sanofi, and UCB; **R. Galimberti** has received honoraria as principal investigator from: Eli Lilly and Company, Janssen, MSD, Novartis, Pfizer, and Roche; **L. F. Eichenfield** has been an advisory board member, and/or speaker, and/or consultant, and/or has participated in clinical studies for: Amgen, AbbVie, Asana, Celgene, Dermavant, Dermira, Eli Lilly and Company, Forte, Galderma, Incyte, Leo Pharma, Matrisys, Menlo, Morphosys/Galapagos, Novartis, Otsuka, Pfizer, Sanofi-Regeneron, and UCB; **R. Bissonnette** has received grants/research support, honoraria, or consulting fees from: AbbVie, Amgen, ApoPharma, Boehringer Ingelheim, Celgene, Dermira, Eli Lilly and Company, Galderma, GSK-Stiefel, Merck, Incyte, Janssen, Kineta, Leo Pharma, Novartis, Pfizer, Tribute, and Xenoport; **B. A. King** has been an advisory board member, and/or speaker, and/or consultant, and/or has participated in clinical studies for: Aclaris Therapeutics, Arena Pharmaceuticals, Concert Pharmaceuticals, Dermavant Sciences, Eli Lilly and Company, Pfizer, Regeneron, and Sanofi Genzyme; **J. P. Thyssen** has been an advisory board member, and/or received speaker honoraria, and/or has participated in clinical studies for: Eli Lilly and Company, Pfizer, and Sanofi-Genzyme; **J. I. Silverberg** has received grants from: GSK, Regeneron-Sanofi, and personal fees from: AbbVie, Eli Lilly and Company, Galderma, Kiniksa Pharmaceuticals, Leo Pharma, Menlo therapeutics, Pfizer, Realm Therapeutics, Regeneron-Sanofi, and Roivant Sciences; **T. Bieber** has received grants as an investigator and honoraria for lecturing, or consulting fees from: AbbVie, Almirall, AnaptysBio, Arena, Asana Biosciences, Astellas, BioVerSys, Boehringer Ingelheim, Celgene, Daichi-Sankyo, Dermavant/Roivant, DermTreat, DS Pharma, Eli Lilly and Company, Evaxion, FLX Bio, Galapagos/MorphoSys, Galderma, Glenmark, GSK, Incyte, Kymab, Leo Pharma, L´Oréal, MenloTx, Novartis, Pfizer, Pierre Fabre, Sanofi-Regeneron, UCB, and Vectans; **K. Kabashima** has received grants or honoraria, or consulting fees from: Maruho, Japan Tobacco, Mitsubishi Tanabe, P&G, Leo Pharma, Ono, Thaiho, and Torii; **Y. Tsunemi** has received lecturer's fees from: Maruho, Sanofi, and Torri Pharmaceutical; **A. Costanzo** has been an advisory board member, and/or speaker, and/or consultant, and/or has participated in clinical studies for: AbbVie, Amgen, Eli Lilly and Company, Janssen, Leo Pharma, Novartis, Pfizer, Sanofi, and UBC; **E. Guttman-Yassky** is an employee of Mount Sinai and has received research funds (grants paid to the institution) from and/or been a consultant for: AbbVie, Almirall, Amgen, AnaptysBio, Asana Biosciences, Boehringer Ingelheim, Cara Therapeutics, Celgene, Concert, DBV, Dermavant, Dermira, DS Biopharma, Eli Lilly and Company, EMD Serono, Escalier, Glenmark, Galderma, Innovaderm, Janssen, Kiniska, Kyowa Kirin, Leo Pharma, Mitsubishi Tanabe, Novan, Pfizer, Ralexar, RAPT Therapeutics, Regeneron, Sanofi, Sienna Biopharma, UCB, and Union Therapeutics; **J. M. Janes**, **A. M. DeLozier**, **M. Gamalo**, **T. Cardillo**, and **F. P. Nunes** are current employees and shareholders of Eli Lilly and Company; **A. S. 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- This study was sponsored by Eli Lilly and Company, under license from Incyte Corporation. Medical writing assistance was provided by Cassandra Haley, PhD, of ProScribe – part of the Envision Pharma Group, and was funded by Eli Lilly and Company
- Previously presented at the World Congress of Dermatology (WCD) 2019 - 24th; Milan, Italy, June 10-15, 2019.