



# Itch and Sleep Improvements with Baricitinib in Patients with Atopic Dermatitis: A Post Hoc Analysis of 3 Phase 3 Studies

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## ABSTRACT

**Introduction:** Burdensome symptoms of atopic dermatitis include itch and sleep disturbance. This post hoc analysis reports the effect of baricitinib on itch and sleep disturbance during the first week of treatment in 3 phase 3 studies.

**Methods:** Patients were randomized 2:1:1:1 to once-daily placebo or baricitinib 1 mg, 2 mg, or 4 mg in the BREEZE-AD1 and -AD2 studies and 1:1:1 to once-daily placebo or baricitinib 2 mg or 4 mg in the BREEZE-AD7 study. Topical corticosteroids were only allowed in BREEZE-AD7. Patients completed the itch numerical rating scale and atopic dermatitis sleep scale (ADSS)

items 1–3 using an electronic daily diary. Data were analyzed by study as least squares mean percent change from baseline in daily scores for the randomized patients. Mixed model repeated measures analysis was used to analyze change from baseline values.

**Results:** A total of 624, 615, and 329 patients were randomized in BREEZE-AD1, -AD2, and -AD7, respectively. Itch severity significantly improved with baricitinib 2 mg and 4 mg versus placebo starting at day 2 (1 day after first dose) in BREEZE-AD1 and -AD7 and at day 1 in BREEZE-AD2. Patients' ability to fall asleep (ADSS item 1) significantly improved with baricitinib 2 mg and 4 mg versus placebo starting at day 2 in all three studies. There were

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significant improvements in patients waking due to itch (ADSS item 2) with baricitinib 4 mg versus placebo starting at day 2 in all three studies. Patients' ability to return to sleep after being woken by itch (ADSS item 3) was significantly improved with baricitinib 4 mg versus placebo starting at day 2 in BREEZE-AD1 and -AD2 and at day 4 in BREEZE-AD7.

**Conclusion:** Rapid onset of action, typically 1 day after taking the first dose of baricitinib, was observed consistently for the burdensome symptoms of itch and sleep disturbance.

**ClinicalTrials.gov identifiers:** BREEZE-AD1, NCT03334396; BREEZE-AD2, NCT03334422; BREEZE-AD7, NCT03733301.

**Keywords:** Atopic dermatitis; Baricitinib; Itch; Patient-reported outcomes; Sleep

### Key Summary Points

#### Why carry out this study?

Burdensome symptoms of atopic dermatitis include itch and sleep disturbances.

The phase 3 BREEZE-AD1, -AD2, and -AD7 studies showed that baricitinib, with or without background topical corticosteroids, improved the signs and symptoms of moderate-to-severe atopic dermatitis compared with placebo.

This post hoc analysis studies the effect of baricitinib on itch and sleep disturbance during the first week of treatment in BREEZE-AD1, -AD2, and -AD7.

#### What was learned from the study?

Baricitinib treatment consistently resulted in a rapid onset of action as early as 1 day after the first dose for the burdensome symptoms of itch and sleep disturbance.

These data support the use of baricitinib with or without background topical corticosteroids for moderate-to-severe atopic dermatitis.

## DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to <https://doi.org/10.6084/m9.figshare.14381201>.

## INTRODUCTION

Atopic dermatitis is a chronic, relapsing, complex immune and inflammatory skin condition characterized by various features of atopy. Approximately 25% of children and 2–7% of adults are affected by atopic dermatitis worldwide [1–3]. Consensus-based European guidelines for the treatment of atopic dermatitis in adults currently recommend education, topical agents, wet wrap therapy, ultraviolet (UV) therapy, psychosomatic counseling, and/or climate therapy for mild-to-moderate disease. For severe disease, hospitalization, cyclosporine A, oral glucocorticosteroids, dupilumab, methotrexate, azathioprine and mycophenolate mofetil, psoralen in combination with UVA, and/or alitretinoin are recommended [4].

The primary symptom for atopic dermatitis is itch (pruritus), which is considered highly bothersome by patients and can be associated with a profound negative impact on quality of life (QoL), manifested as poor overall health and dissatisfaction with life [5]. In a study of 380 participants with moderate-to-severe atopic dermatitis, itch frequency was reported as a problem by 86% of participants, and 42% reported itching  $\geq 18$  h/day [6]. Very few patients experience an absence of itch for more than 1 week at a time [6, 7]. This itching results in scratching, which in turn leads to skin damage, an increased risk of cutaneous infections, and even more itching (the vicious itch–scratch cycle) [8].

The majority of patients with atopic dermatitis experience itch during the evening and at night, which causes difficulty in falling asleep in over 80% of patients, as well as frequent nighttime awakenings [7, 9]. This leads to daytime fatigue, irritability, disturbed cognition,

and decreased motor performance [7, 9]. Furthermore, poorer sleep has been shown to be associated with increased disease severity in atopic dermatitis [10].

Due to the substantial impact of itch on the QoL of patients with atopic dermatitis, treatments are needed that provide rapid relief as well as durable, long-term control of itch [11]. Several immunomodulatory agents are under investigation for the treatment of atopic dermatitis. Baricitinib, an oral selective Janus kinase (JAK)1/JAK2 inhibitor [12], is indicated in the European Union and is being evaluated in the USA and other countries for the treatment of moderate-to-severe atopic dermatitis in adult patients who are candidates for systemic therapy. The phase 3, randomized BREEZE-AD1, -AD2, and -AD7 studies investigated oral baricitinib as monotherapy (BREEZE-AD1 and -AD2) and in combination with topical corticosteroids (BREEZE-AD7). Baricitinib significantly improved the signs and symptoms of moderate-to-severe atopic dermatitis compared with placebo at 16 weeks [13, 14]. In all three studies, baricitinib was found to be well tolerated [13, 14].

Due to the detrimental effects of atopic dermatitis on QoL, patients require relief of symptoms as rapidly as possible. Therefore, this post hoc analysis reports the effect of baricitinib on itch and sleep disturbance during the first week of treatment in the BREEZE-AD1, -AD2, and -AD7 studies.

## METHODS

### Study design

The study designs, patients, assessments, randomization and masking methods, procedures, and outcomes for BREEZE-AD1, -AD2, and -AD7 have been published previously [13, 14]. In brief, all three studies included patients with moderate-to-severe atopic dermatitis who had an inadequate response to existing topical therapies; BREEZE-AD1 and -AD2 also allowed patients who were intolerant to topical therapies. In BREEZE-AD1 and -AD2, patients were randomized 2:1:1:1 to once-daily placebo or

baricitinib 1 mg, 2 mg, or 4 mg for 16 weeks. In BREEZE-AD7, patients were randomized 1:1:1 to once-daily placebo or baricitinib at 2 mg or 4 mg for 16 weeks, and the use of low-to-moderate potency topical corticosteroids was allowed for active lesions.

The studies were approved by all local institutions of the study sites. Details of the institutions and their ethics committees have been previously published [13, 14]. The studies were performed in accordance with the Declaration of Helsinki 1964 and its later amendments. All subjects provided informed consent to participate in the study.

### Patient-reported outcomes

An electronic daily diary was used to assess symptoms in the previous 24 h. Patients completed multiple items, including the itch Numerical Rating Scale (NRS) (measuring the worst itch from 0 = no itch to 10 = worst itch imaginable) [15] and Atopic Dermatitis Sleep Scale (ADSS) items 1–3 [16]. The ADSS item 1 asks, “How difficult was it to fall asleep last night because of your itch?”; ADSS item 2 asks, “How many times did your itch cause you to wake up last night?”; and ADSS item 3 asks, “Overall, how difficult was it to get back to sleep last night because of your itch?”. Only those who responded  $\geq 1$  for ADSS item 2 were allowed to respond to ADSS item 3. Patients rated ADSS items 1 and 3 using a 5-point Likert-type scale with response options ranging from 0 = not at all to 4 = very difficult. Patients rated ADSS item 2 by selecting the number of times they woke up each night due to itch, ranging from 0 to 29 times. The overall severity of a patient’s itching was indicated by selecting the number that best described the worst level of itching in the past 24 h. The ADSS was completed each day for patients’ sleep the previous night. Each item was scored individually. Patients were recommended to take the study medication at approximately the same time every day, usually at the start of the day. As patient diaries were used to assess symptoms in the previous 24 h, patients could report changes

in symptoms as early as the first day of treatment.

### Statistical analysis

In this post hoc analysis, the changes from baseline in itch NRS and ADSS items 1–3 were analyzed for all patients randomized from day 1 to day 7 in the intention-to-treat population by study. Data after any rescue therapy or discontinuation were excluded from the analysis. A mixed model repeated measures analysis was applied to the change from baseline and included treatment, region, baseline disease severity, and visit. The treatment-by-visit-interactions were fixed as categorical effects, and the baseline and baseline-by-visit-interactions were fixed as continuous effects with the baseline value designated as the mean of the seven daily assessments prior to the date of first study drug dose. The treatment comparisons were reported as least squares mean percent change from baseline and derived as follows: [least squares mean change from baseline obtained from the mixed model repeated measures analysis/overall mean at baseline]  $\times$  100. *P* values for treatment comparisons were not controlled by multiplicity. All data were analyzed with SAS version 9.4 (SAS Institute, Cary, NC, USA).

## RESULTS

### Patients

A total of 624, 615, and 329 patients were randomized in BREEZE-AD1, -AD2, and -AD7, respectively. The baseline demographics and disease characteristics were balanced among treatment groups in all three studies (Table 1).

### Rapid improvement in itch

In BREEZE-AD1, -AD2, and -AD7, treatment with baricitinib 2 mg and 4 mg resulted in statistically significant improvements in least squares mean percentage change from baseline in itch NRS compared with placebo starting at day 2 (1 day after first dose) and continuing

through day 7, except for baricitinib 2 mg at day 3 in BREEZE-AD7. Statistically significant improvements in itch NRS compared with placebo were also observed during the first week of treatment with baricitinib 1 mg in BREEZE-AD1 and -AD2. At day 7, the greatest improvements in itch NRS in BREEZE-AD1, -AD2, and -AD7 were  $-25.7$ ,  $-18.4$ , and  $-37.8\%$ , respectively, each with baricitinib 4 mg (Fig. 1).

### Rapid improvement in ability to fall asleep

In BREEZE-AD1, -AD2, and -AD7, baricitinib 2 mg and 4 mg resulted in statistically significant improvements in least squares mean percent change from baseline in ADSS item 1 compared with placebo starting at day 2 and continuing through day 7. Statistically significant improvements in ADSS item 1 compared with placebo were also observed during the first week of treatment with baricitinib 1 mg in BREEZE-AD1 and -AD2. At day 7, the greatest improvements in ADSS item 1 in BREEZE-AD1, -AD2, and -AD7 were  $-33.5$ ,  $-24.5$ , and  $-52.6\%$ , respectively, each with baricitinib 4 mg (Fig. 2).

### Rapid reduction in nightly awakenings

In BREEZE-AD1, -AD2, and -AD7, baricitinib 4 mg resulted in a statistically significant improvement in least squares mean percent change from baseline in ADSS item 2 compared with placebo starting at day 2 and continuing through day 7. Statistically significant improvements in ADSS item 2 compared with placebo were also observed during the first week of treatment with baricitinib 1 mg and 2 mg in BREEZE-AD1 and -AD2 and baricitinib 2 mg in BREEZE-AD7. At day 7, the greatest improvements in ADSS item 2 in BREEZE-AD1, -AD2, and -AD7 were  $-41.9$ ,  $-45.1$ , and  $-67.8\%$ , respectively, each with baricitinib 4 mg (Fig. 3).

### Rapid improvement in returning to sleep

In BREEZE-AD1 and -AD2, baricitinib 4 mg resulted in a statistically significant

**Table 1** Baseline patient demographics and disease characteristics

	BREEZE-AD1				BREEZE-AD2				BREEZE-AD7			
	Placebo, N = 249	Baricitinib 1 mg N = 127	Baricitinib 2 mg N = 123	Baricitinib 4 mg N = 125	Placebo N = 244	Baricitinib 1 mg N = 125	Baricitinib 2 mg N = 123	Baricitinib 4 mg N = 123	Placebo + TCS N = 109	Baricitinib 2 mg + TCS N = 109	Baricitinib 4 mg + TCS N = 111	
Age (years)	35 (12.6)	36 (12.4)	35 (13.7)	37 (12.9)	35 (13.0)	33 (10.0)	36 (13.2)	34 (14.1)	34 (13.2)	34 (12.8)	34 (11.4)	
Female, n (%)	101 (40.6)	49 (38.6)	41 (33.3)	42 (33.6)	90 (36.9)	45 (36.0)	58 (47.2)	41 (33.3)	38 (34.9)	39 (35.8)	36 (32.4)	
Race, n (%)												
Caucasian	147 (59.5)	74 (58.3)	75 (61.0)	70 (56.5)	169 (69.3)	85 (68.0)	85 (69.1)	82 (66.7)	46 (42.2)	50 (45.9)	54 (48.6)	
Asian	73 (29.6)	40 (31.5)	35 (28.5)	41 (33.1)	72 (29.5)	36 (28.8)	37 (30.1)	38 (30.9)	57 (52.3)	57 (52.3)	54 (48.6)	
Duration since AD diagnosis (years)	26 (15.5)	27 (14.9)	25 (14.6)	25 (14.9)	25 (13.9)	24 (12.7)	24 (13.8)	23 (14.8)	22.0 (12.2)	24.6 (14.8)	25.5 (13.2)	
Weight (kg)	73 (15.7)	74 (17.2)	75 (17.7)	74 (17.2)	72 (15.5)	75 (16.6)	72 (14.7)	73 (14.9)	73 (15.8)	72 (15.5)	73 (17.8)	
Body mass index (kg/m <sup>2</sup> )	25 (4.5)	25 (4.6)	25 (5.1)	25 (4.3)	25 (4.3)	26 (5.2)	25 (5.0)	25 (4.2)	26 (4.6)	25 (4.7)	25 (5.1)	
Geographic region, n (%)												
Europe <sup>a</sup>	135 (54.2)	67 (52.8)	67 (54.5)	68 (54.4)	111 (45.5)	57 (45.6)	56 (45.5)	56 (45.5)	38 (34.9)	38 (34.9)	39 (35.1)	
Japan	45 (18.1)	23 (18.1)	21 (17.1)	22 (17.6)	45 (18.4)	22 (17.6)	22 (17.9)	23 (18.7)	21 (19.3)	20 (18.3)	22 (19.8)	
Other <sup>b</sup>	69 (27.7)	37 (29.1)	35 (28.5)	35 (28.0)	88 (36.1)	46 (36.8)	45 (36.6)	44 (35.8)	50 (45.9)	51 (46.8)	50 (45.0)	
vIGA-AD <sup>c</sup> score of 4, n (%)	105 (42.2)	53 (41.7)	52 (42.3)	51 (40.8)	121 (49.6)	63 (50.8)	62 (50.4)	63 (51.2)	48 (44.4)	50 (45.9)	50 (45.0)	
EASI <sup>d</sup>	32 (13.0)	29 (11.8)	31 (11.7)	32 (12.7)	33 (12.8)	33 (12.7)	35 (16.0)	33 (12.7)	29 (12.3)	29 (11.9)	31 (12.6)	
SCORAD <sup>e</sup>	68 (14.0)	66 (14.4)	68 (13.0)	68 (12.9)	68 (12.7)	67 (12.9)	69 (13.3)	68 (13.6)	66.6 (13.8)	66.8 (14.0)	68.3 (13.2)	
Body surface area affected	53 (23.1)	47 (21.2)	50 (22.1)	52 (21.8)	52 (21.7)	55 (21.9)	55 (26.1)	54 (21.5)	48.1 (24.4)	50.6 (21.6)	52.1 (23.3)	
Itch NRS <sup>f</sup>	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)	7.4 (1.7)	7.0 (2.1)	7.0 (2.0)	
Skin pain NRS <sup>g</sup>	6.1 (2.5)	5.5 (2.4)	5.7 (2.6)	5.7 (2.4)	6.2 (2.5)	5.7 (2.7)	6.2 (2.5)	6.0 (2.6)	6.8 (2.3)	6.3 (2.5)	6.0 (2.5)	
ADSS item 1 <sup>h</sup>	2.0 (1.1)	1.8 (1.0)	1.9 (1.1)	1.9 (1.0)	1.9 (1.2)	1.8 (1.1)	1.9 (1.1)	1.9 (1.1)	2.3 (1.1)	2.1 (1.1)	2.1 (1.0)	
ADSS item 2 <sup>i</sup>	3.4 (5.2)	2.5 (3.4)	2.3 (4.1)	3.3 (5.2)	1.8 (2.1)	1.6 (1.8)	2.1 (2.9)	1.9 (2.5)	1.8 (2.0)	1.9 (2.3)	1.8 (2.3)	
ADSS item 3 <sup>j</sup>	2.2 (1.0)	2.1 (0.9)	2.3 (1.0)	2.2 (0.9)	2.2 (1.0)	2.2 (1.0)	2.2 (1.0)	2.3 (0.9)	2.5 (0.9)	2.4 (1.0)	2.4 (0.8)	
POEM <sup>k</sup>	21 (5.6)	20 (5.6)	21 (5.6)	21 (5.6)	21 (6.3)	20 (6.5)	21 (6.0)	20 (6.3)	20.9 (6.7)	21.0 (6.3)	21.4 (6.0)	

Table 1 continued

Baseline study characteristics	BREEZE-AD1			BREEZE-AD2			BREEZE-AD7			
	Placebo N = 249	Baricitinib 1 mg N = 127	Baricitinib 2 mg N = 123	Baricitinib 4 mg N = 125	Placebo N = 244	Baricitinib 1 mg N = 125	Baricitinib 2 mg N = 123	Baricitinib 4 mg N = 123	Placebo + TCS N = 109	Baricitinib 2 mg + TCS N = 109
DLQI <sup>l</sup>	14 (7.4)	13 (6.8)	13 (7.7)	14 (7.1)	15 (8.1)	14 (7.7)	14 (8.4)	15.0 (7.9)	15.0 (7.7)	14.7 (7.9)

Data are presented as the mean (SD) unless otherwise indicated. Data for race excludes patients who were not Caucasian or Asian

AD Atopic dermatitis, ADSS Atopic Dermatitis Sleep Scale, DLQI Dermatology Life Quality Index, EASI Eczema Area and Severity Index, N number of patients, n number of patients in a subgroup, NRS numeric rating scale, POEM Patient Oriented Eczema Measures, SCORAD SCORing Atopic Dermatitis, SD standard deviation, TCS topical corticosteroids, vIGA-AD Validated Investigator Global Assessment for Atopic Dermatitis

<sup>a</sup> Europe: BREEZE-AD1: Czech Republic, Denmark, France, Germany, and Italy; BREEZE-AD2: Austria, Hungary, Poland, Spain, and Switzerland; BREEZE-AD7: Austria, Germany, Italy, Poland, and Spain

<sup>b</sup> Other: BREEZE-AD1: India, Mexico, Russia, and Taiwan; BREEZE-AD2: Argentina, Australia, Israel, and South Korea; BREEZE-AD7: Argentina, Australia, Japan, South Korea, and Taiwan

<sup>c</sup> vIGA-AD measures the investigator's global assessment of disease severity based on a static 5-point scale from 0 (clear skin) to 4 (severe disease)

<sup>d</sup> EASI scores range from 0 to 72, with higher scores indicating greater severity

<sup>e</sup> SCORAD is a combined score of investigator-reported disease severity and affected body surface area and patient-reported symptoms of itch and sleep dysfunction; scores range from 0–103

<sup>f</sup> Itch NRS, ranging from 0 (no itch) to 10 (worst itch imaginable)

<sup>g</sup> Skin Pain NRS, ranging from 0 (no pain) to 10 (worst pain)

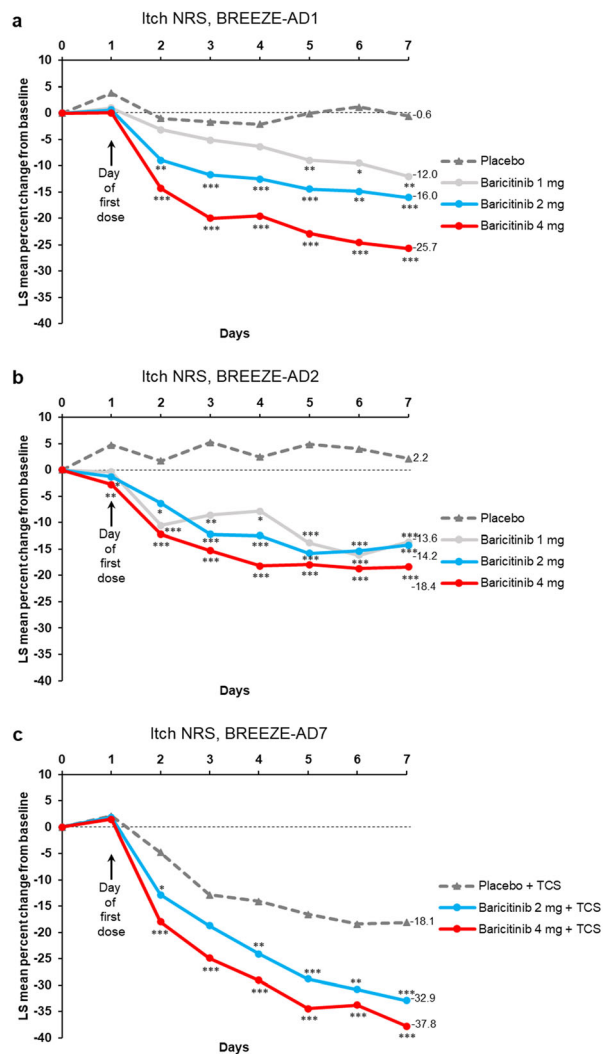
<sup>h</sup> ADSS item 1 assesses how difficult it was to fall asleep the previous night due to itch using a 5-point Likert-type scale with response options ranging from 0 = not at all to 4 = very difficult

<sup>i</sup> ADSS item 2 assesses the frequency of nighttime awakenings due to itch the previous night on a scale of 0–29

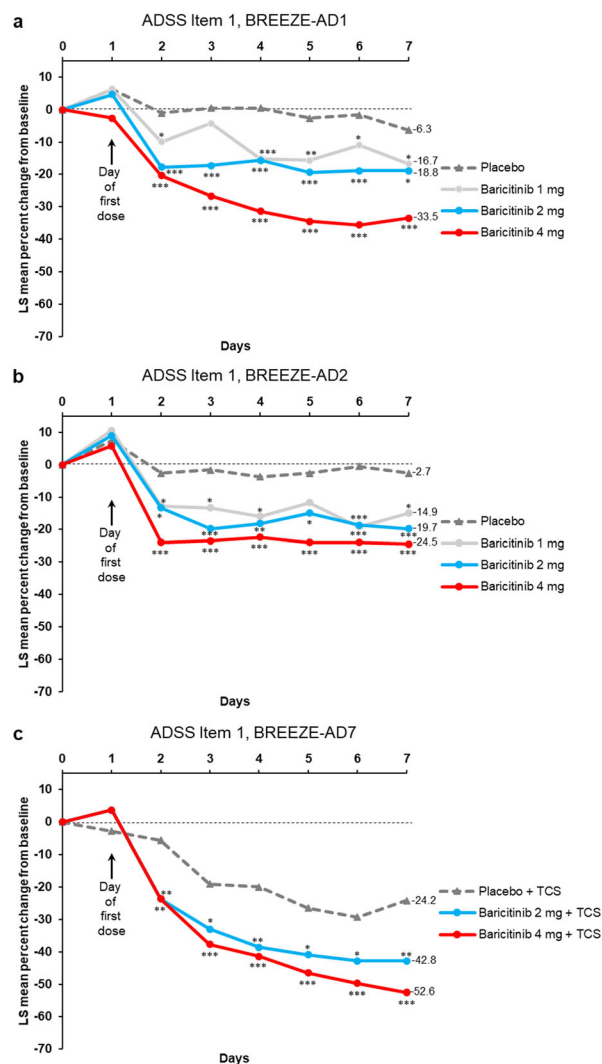
<sup>j</sup> ADSS item 3 assesses how difficult it was to get back to sleep the previous night due to itch using a 5-point Likert-type scale with response options ranging from 0 = not at all to 4 = very difficult

<sup>k</sup> POEM is a composite measure of patient-reported symptoms, including the effect of symptoms on sleep and evaluates the frequency of symptoms (including itch) and the effect of atopic dermatitis on sleep on a scale of 0–28

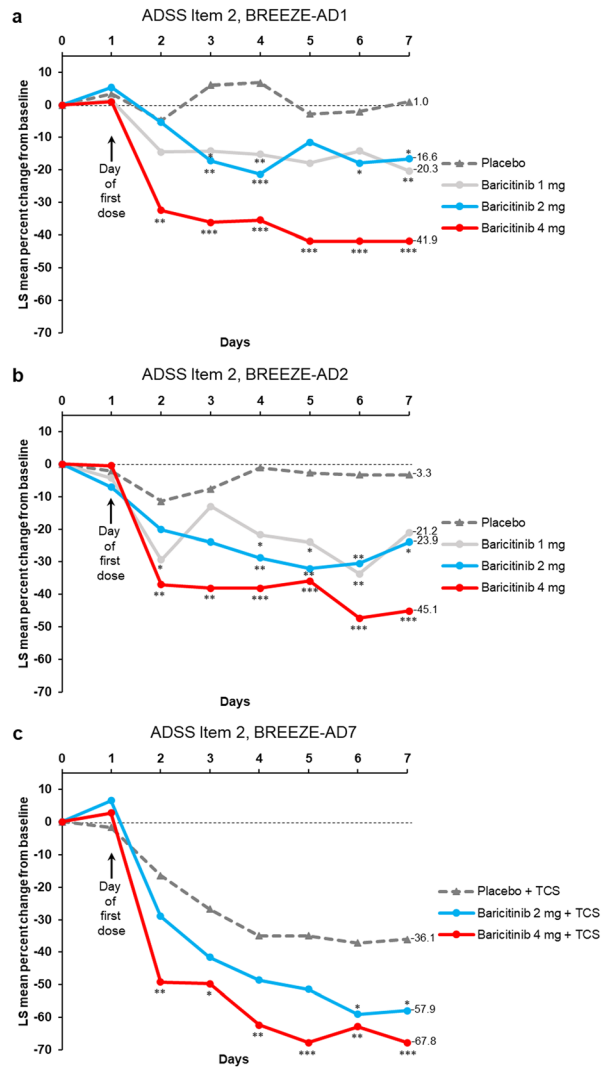
<sup>l</sup> DLQI evaluates health-related quality of life on a scale of 0–30



**Fig. 1** Least squares mean percent change from baseline in itch NRS during the first week of treatment in BREEZE-AD1 (a), BREEZE-AD2 (b), and BREEZE-AD7 (c). The number of patients assessed at each time point ranged from 215–240 for placebo, 111–125 for baricitinib 1 mg, 113–117 for baricitinib 2 mg, and 115–121 for baricitinib 4 mg in BREEZE-AD1; 208–232 for placebo, 101–115 for baricitinib 1 mg, 112–116 for baricitinib 2 mg, and 113–120 for baricitinib 4 mg in BREEZE-AD2; and 104–105 for placebo, 104–107 for baricitinib 2 mg, and 103–107 for baricitinib 4 mg in BREEZE-AD7. Asterisks indicate significant difference compared to placebo at: \* $P \leq 0.05$ , \*\* $P \leq 0.01$ , and \*\*\* $P < 0.001$ . *LS* least squares, *NRS* numeric rating scale, *TCS* topical corticosteroids



**Fig. 2** Least squares mean percent change from baseline in ADSS item 1 during the first week of treatment in BREEZE-AD1 (a), BREEZE-AD2 (b), and BREEZE-AD7 (c). The number of patients assessed at each time point ranged from 215–240 for placebo, 111–125 for baricitinib 1 mg, 113–117 for baricitinib 2 mg, and 115–121 for baricitinib 4 mg in BREEZE-AD1; 208–232 for placebo, 101–115 for baricitinib 1 mg, 112–116 for baricitinib 2 mg, and 113–120 for baricitinib 4 mg in BREEZE-AD2; and 104–105 for placebo, 104–107 for baricitinib 2 mg, and 103–107 for baricitinib 4 mg in BREEZE-AD7. Asterisks indicate significant difference compared to placebo at: \* $P \leq 0.05$ , \*\* $P \leq 0.01$ , and \*\*\* $P < 0.001$ . *LS* least squares, *TCS* topical corticosteroids



**Fig. 3** Least squares mean percent change from baseline in ADSS item 2 during the first week of treatment in BREEZE-AD1 (a), BREEZE-AD2 (b), and BREEZE-AD7 (c). The number of patients assessed at each time point ranged from 215–240 for placebo, 111–125 for baricitinib 1 mg, 113–117 for baricitinib 2 mg, and 115–121 for baricitinib 4 mg in BREEZE-AD1; 208–232 for placebo, 101–115 for baricitinib 1 mg, 112–116 for baricitinib 2 mg, and 113–120 for baricitinib 4 mg in BREEZE-AD2; and 104–107 for placebo, 104–107 for baricitinib 2 mg, and 103–107 for baricitinib 4 mg in BREEZE-AD7. Asterisks indicate significant difference compared to placebo at: \* $P \leq 0.05$ , \*\* $P \leq 0.01$ , and \*\*\* $P < 0.001$ . *LS* least squares, *TCS* topical corticosteroids

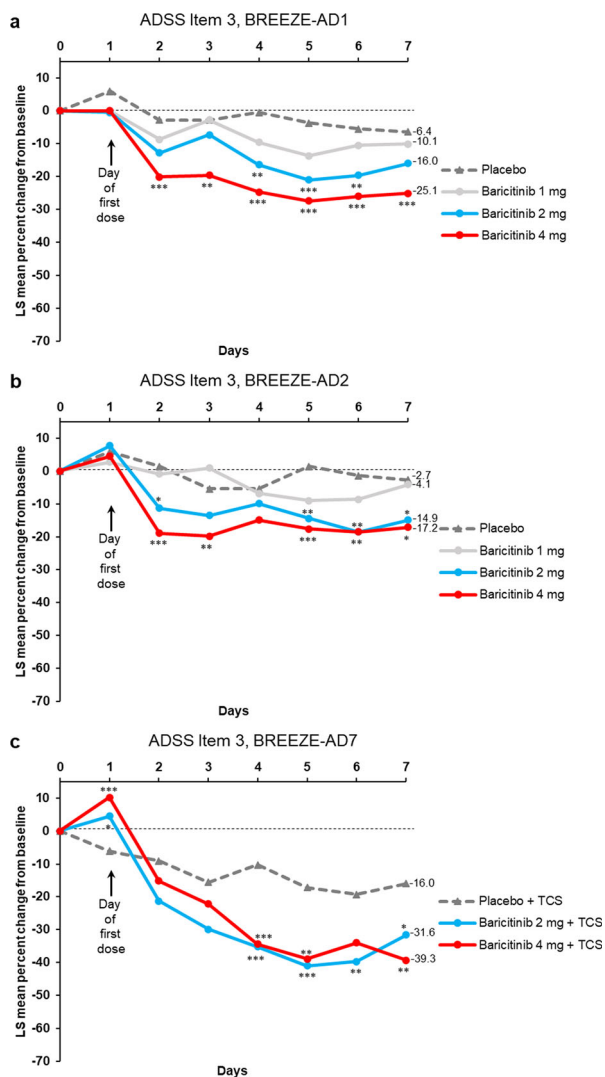
improvement in least squares mean percent change from baseline in ADSS item 3 compared with placebo starting at day 2 and continuing through day 7. In BREEZE-AD7, baricitinib 4 mg resulted in a statistically significant improvement in ADSS item 3 compared with placebo on days 4, 5, and 7. Statistically significant improvements in ADSS item 3 compared with placebo were also observed during the first week of treatment with baricitinib 2 mg in all three studies. At day 7, the greatest improvements in ADSS item 3 in BREEZE-AD1, -AD2, and -AD7 were  $-25.1$ ,  $-17.2$ , and  $-39.3\%$ , respectively, each with baricitinib 4 mg (Fig. 4).

## DISCUSSION

The phase 3 BREEZE-AD1, -AD2, and -AD7 studies showed that baricitinib, with or without topical corticosteroids, significantly improved the signs and symptoms of moderate-to-severe atopic dermatitis compared with placebo at 16 weeks [13, 14]. This post hoc analysis adds to the previously reported findings for BREEZE-AD1, -AD2, and -AD7 and shows that the onset of baricitinib is rapid with improvements in the burdensome symptoms of itch and sleep disturbance, typically reported as early as 1 day after the first dose (i.e., day 2).

As discussed above, many patients experience itch in the evening and at night, which causes sleep difficulties and substantially impacts QoL [7, 9, 17]. Consequently, it is critical for patients' wellbeing and QoL that treatments for atopic dermatitis provide relief of symptoms as quickly as possible. This analysis demonstrates that daily assessment of patient-reported outcomes allows for the detection of early improvements. Itch significantly improved with baricitinib 2 mg and 4 mg versus placebo starting at day 2 in BREEZE-AD1 and -AD7 and at day 1 in BREEZE-AD2. In all three studies, patients' ability to fall asleep (ADSS item 1) significantly improved with baricitinib 2 mg and 4 mg versus placebo starting at day 2, and there were significant improvements in patients' waking due to itch (ADSS item 2) with baricitinib 4 mg versus placebo starting at day 2. Furthermore, patients' ability to return to sleep





**Fig. 4** Least squares mean percent change from baseline in ADSS item 3 during the first week of treatment in BREEZE-AD1 (a), BREEZE-AD2 (b), and BREEZE-AD7 (c). The number of patients assessed at each time point ranged from 158–183 for placebo, 65–81 for baricitinib 1 mg, 60–74 for baricitinib 2 mg, and 59–83 for baricitinib 4 mg in BREEZE-AD1; 124–156 for placebo, 52–75 for baricitinib 1 mg, 59–74 for baricitinib 2 mg, and 57–76 for baricitinib 4 mg in BREEZE-AD2; and 48–70 for placebo, 47–74 for baricitinib 2 mg, and 28–65 for baricitinib 4 mg in BREEZE-AD7. Asterisks indicate significant difference compared to placebo at: \* $P \leq 0.05$ , \*\* $P \leq 0.01$ , and \*\*\* $P < 0.001$ . ADSS atopic dermatitis sleep scale, LS least squares, TCS topical corticosteroids

after being woken by itch (ADSS item 3) was significantly improved with baricitinib 4 mg versus placebo starting at day 2 in BREEZE-AD1 and -AD2 and at day 4 in BREEZE-AD7. Significant improvements were observed more consistently with the baricitinib 4 mg dose compared with the baricitinib 2 mg dose. These data show that baricitinib provides a rapid onset of efficacy, typically 1 day after taking the first dose, for the burdensome symptoms of itch and sleep disturbance. These findings, which show responses to baricitinib are rapid, complement the primary outcome data, indicating that responses to baricitinib are also durable [13, 14].

Several other JAK inhibitors that are approved or under investigation (both oral and topical formulations) for the treatment of atopic dermatitis are also being investigated for rapid onset of action for itch [18–22]. While these studies are not head-to-head and do not allow direct comparison of different agents, collectively they suggest that JAK inhibitors are an efficacious therapeutic option with a rapid onset of action in patients with atopic dermatitis.

One limitation of this study was that, unlike full sleep studies or actigraphy, the measures reported by study participants were not objective and may not have been self-assessed or reported consistently. Hence, the data should be interpreted with caution. A strength of this study was the consistency in results across the three separate phase 3 studies.

## CONCLUSIONS

Baricitinib treatment consistently resulted in a rapid onset of action, typically 1 day after the first dose, in the improvement of the clinically burdensome symptoms of itch and sleep disturbance. Together with the primary outcome data [13, 14] and safety profile [23], the findings from this study support the use of baricitinib, with or without topical corticosteroids, in the treatment of moderate-to-severe atopic dermatitis.

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**Compliance with ethics guidelines.** The studies were approved by all institutions. Details of the institutions and their ethics committees have been previously published [13, 14]. The studies were performed in accordance with the Declaration of Helsinki 1964 and its later amendments. All subjects provided informed consent to participate in the study.

**Data availability.** Eli Lilly 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 USA and EU 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 <http://www.vivli.org>.

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