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Efficacy and safety of baricitinib in combination with topical corticosteroids in patients with moderate-to-severe atopic dermatitis with inadequate response, intolerance or contraindication to ciclosporin: results from a randomized, placebo-controlled, phase III clinical trial (BREEZE-AD4)*

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Summary

Background Baricitinib, an oral selective Janus kinase (JAK)1 and JAK 2 inhibitor, was shown to improve the signs and symptoms of moderate-to-severe atopic dermatitis (AD).

Objectives To evaluate the efficacy and safety of baricitinib with background topical corticosteroids (TCS) in patients with moderate-to-severe AD and inadequate response, intolerance or contraindication to ciclosporin A (CA).

Methods In this double-blind, randomized, placebo-controlled, phase III study, patients were randomized 1: 1: 2: 1 to placebo (N = 93), baricitinib 1 mg (N = 93), 2 mg (N = 185) or 4 mg (N = 92) with background TCS. The primary endpoint was the proportion of patients receiving baricitinib 4 mg or 2 mg (+ TCS) vs. placebo + TCS who achieved ≥ 75% improvement from baseline in the Eczema Area and Severity Index (EASI 75) at week 16.

Results Baricitinib 4 mg + TCS was superior to placebo + TCS for EASI 75 (4 mg: 32%, placebo: 17%, P = 0·031) at week 16 and for improvements in itch, skin pain and number of night-time awakenings owing to itch. Improvements were maintained through 52 weeks of treatment. Treatment-emergent adverse events (TEAEs) were more common with baricitinib than placebo (+ TCS); most were mild or moderate. The most frequent TEAEs with baricitinib 4 mg + TCS were nasopharyngitis, herpes simplex, influenza and headache. No deaths or deep vein thromboses were reported.

Conclusions Baricitinib 4 mg + TCS improved the signs and symptoms of moderate-to-severe AD through 52 weeks of treatment in patients with inadequate response, intolerance or contraindication to CA. The safety profile was consistent with previous studies of baricitinib in moderate-to-severe AD.

What is already known about this topic?

- Ciclosporin A is indicated for the treatment of atopic dermatitis that is refractory to topical therapies. However, its use is limited by safety concerns and it may not provide adequate response for some patients.
- Baricitinib, an oral selective Janus kinase (JAK)1 and JAK2 inhibitor, has been shown to improve the signs and symptoms of moderate-to-severe atopic dermatitis as a monotherapy or in combination with topical corticosteroids.

What does this study add?

- Baricitinib combined with background low- or moderate-potency topical corticosteroids provided improvements in the signs and symptoms of moderate-to-severe atopic dermatitis through 1 year of treatment in patients with a contraindication, intolerance or failure to respond to ciclosporin A.
- The most common treatment-emergent adverse events with baricitinib 4 mg were nasopharyngitis, herpes simplex, influenza and headache.
- The safety profile was consistent with previous studies in patients with moderate-to-severe atopic dermatitis.

Atopic dermatitis (AD) is a common, chronic and inflammatory skin disease characterized by severe pruritus and recurrent eczematous lesions and is associated with poor health-related quality of life, sleep disturbance, diminished productivity and social/emotional distress.[1–5] Emollients and topical corticosteroids (TCS) are recommended first-line treatments for AD.[6,7] Systemic treatments are used (often with background TCS) for moderate or severe AD that is refractory to TCS.[8–10] Conventional systemic treatments such as ciclosporin A (CA) have variable efficacy and have safety concerns that may limit their use to short-term treatment.[8–10] AD is a complex disease for which an expanding drug pipeline is on the way; hopefully, this will address the heterogeneous response to established therapies.[11] Dupilumab, an anti-interleukin-4-receptor-α antibody, which was recently approved for moderate-to-severe AD, provides a new therapeutic option but is not effective in all patients and requires subcutaneous injection.[12,13] There remains an unmet need for additional efficacious, well-tolerated and convenient systemic therapies for AD.

Baricitinib, an oral selective Janus kinase (JAK)1 and JAK 2 inhibitor, is approved in many countries for moderate-to-severe AD in adult patients who are candidates for systemic therapy and is being studied in the USA and other countries. Baricitinib improved the signs and symptoms of moderate-to-severe AD in four phase III studies as a monotherapy (BREEZE-AD1, BREEZE-AD2 and BREEZE-AD5) and with background TCS (BREEZE-AD7).[14–16] The objective of the current study (BREEZE-AD4) was to evaluate the efficacy and safety of baricitinib with background TCS in patients with moderate-to-severe AD and inadequate response, intolerance or contraindication to CA.

Patients and methods

Patients

Participants were adults with moderate-to-severe AD [Eczema Area and Severity Index (EASI) ≥ 16, validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD™) ≥ 3, and body surface area (BSA) involvement ≥10%] with a history of inadequate response to TCS and inadequate response, contraindication or intolerance to CA. Patients were excluded if they had concomitant skin disease that would interfere with efficacy evaluations, side-effects to TCS that would prevent their use, or concomitant illness requiring systemic corticosteroids. Complete eligibility criteria are provided in Appendix S1 (see Supporting Information).

Study design

BREEZE-AD4 is a multicentre, double-blind, randomized, placebo-controlled, phase III study. During a 52-week double-blind treatment period, patients were randomized 1: 1: 2: 1 to placebo, baricitinib 1 mg, 2 mg or 4 mg, administered orally once per day. Patients enrolled at 102 sites across 14 countries (Austria, Belgium, Brazil, Finland, France, Germany, Italy, Japan, Netherlands, Poland, Russia, Spain, Switzerland and the UK). Daily use of background emollients was required. Patients were instructed to use background low- or moderate-potency TCS on active lesions.

Patients whose lesions persisted or worsened despite emollient and TCS use or who required prolonged application of moderate-potency TCS on large surfaces were considered for rescue therapy with high- or ultrahigh-potency TCS.

Phototherapy and systemic therapies for AD were allowed only as rescue therapy. Patients receiving rescue therapy with high- or ultrahigh-potency TCS or phototherapy could remain in the trial, but investigational product interruption was required upon rescue to phototherapy. Rescue to systemic therapies required permanent treatment discontinuation. Additional details on study design are provided in Appendix S1.

BREEZE-AD4 (ClinicalTrials.gov: NCT03428100) was conducted in accordance with the ethical principles of the Declaration of Helsinki. The study was approved by the ethical review board at each participating site. Study participants provided written informed consent prior to performing study procedures.

Outcomes

The primary objective of this study was to determine whether baricitinib 4 mg or 2 mg (+ TCS) was superior to placebo + TCS for treatment of moderate-to-severe AD as measured by the proportion of patients achieving ≥75% improvement from baseline in EASI (EASI 75) at week 16. Key secondary objectives of the study were to compare the efficacy of baricitinib with placebo (+ TCS) as measured by improvements in skin inflammation and patient-reported outcome (PRO) measures through week 24. Efficacy endpoints are listed in Table S1 (see Supporting Information).

Safety outcomes included laboratory tests, vital signs, physical examination findings and adverse events (AEs). An independent data monitoring committee consisting of members external to the sponsor conducted regular reviews of safety findings. A blinded clinical event committee adjudicated potential major adverse cardiovascular events (cardiovascular death, myocardial infarction and stroke), other cardiovascular events, venous thrombotic events and noncardiovascular deaths. Details of study outcomes are provided in Appendix S1.

Statistical analyses

A graphical multiple-testing procedure was implemented for the primary and key secondary endpoints to control the overall familywise type I error rate at a two-sided alpha level of 0·05 (Figure S1; see Supporting Information). There was no adjustment for multiple comparisons for other analyses.

Efficacy analyses were performed on the intent-to-treat population and included all randomized patients. Categorical efficacy outcomes were analysed using a logistic regression analysis with geographical region (see Appendix S1 for details), baseline disease severity, baseline value of endpoint variable and treatment group in the model. Continuous outcomes were analysed using mixed model repeated measures (MMRM) analysis with treatment, region, baseline disease severity, visit and treatment-by-visit interaction as fixed categorical effects and baseline and baseline-by-visit-interaction as fixed continuous effects.

Two censoring rules were applied to efficacy results to exclude data in predefined circumstances. With the primary censoring rule, data were considered as missing after permanent study drug discontinuation or after rescue therapy, regardless of the duration or timing of the rescue therapy. With the secondary censoring rule, data were considered as missing after permanent study drug discontinuation only. Nonresponder imputation (NRI) was used after applying censoring for categorical endpoints. For continuous outcomes, after observations were set to missing, MMRM analysis was used. In addition, for analyses of efficacy through week 52 (weeks 0–52), modified last observation carried forward (mLOCF) was used for continuous (prespecified) and categorical (post hoc) outcomes, after applying the secondary censoring rule.

Safety was summarized using descriptive statistics for all randomized patients who received at least one dose of investigational product according to the treatment regimen to which they were assigned and did not discontinue from the study for the reason of 'lost to follow-up' at the first postbaseline visit. Additional details on statistical analyses are provided in Appendix S1.

Results

Overall, 463 patients were randomized to placebo (N = 93), baricitinib 1 mg (N = 93), 2 mg (N = 185) or 4 mg (N = 92) with background TCS (Figure 1a). The proportions of patients at week 16, 24 and 52 who completed the respective study visits (with and without rescue therapy) or discontinued early are presented in Figure 1b–d. Baseline demographics and disease characteristics were well balanced between treatment groups (Table 1). CA history at baseline is summarized in Table S2 (see Supporting Information).

Primary endpoint

Baricitinib 4 mg + TCS met the primary endpoint of superiority to placebo + TCS for EASI 75 (4 mg: 32%, placebo: 17%; P = 0·031) at week 16. Baricitinib 2 mg + TCS was not superior to placebo + TCS for EASI 75 at week 16 (28%, P = 0·072). Table 2 presents efficacy endpoints through week 24 of BREEZE-AD4 (primary censoring rule, NRI and MMRM).

Key secondary endpoints

Baricitinib 1 mg + TCS was not superior to placebo + TCS for EASI 75 at week 16. Baricitinib 4 mg + TCS was superior to placebo + TCS for the mean percentage change from baseline in EASI (EASI PCFB) at week 16 (P < 0·001), ≥ 4-point improvement from baseline in the Itch Numeric Rating Scale (NRS) at week 2 (P = 0·002), week 4 (P < 0·001) and week 16 (P < 0·001), mean change from baseline (CFB) in the Skin Pain NRS at week 16 (P < 0·001), and mean CFB in the number of night-time awakenings owing to itch as measured by the Atopic Dermatitis Sleep Scale (ADSS) item 2 at week 16 (P < 0·001). Baricitinib 4 mg + TCS was not superior to

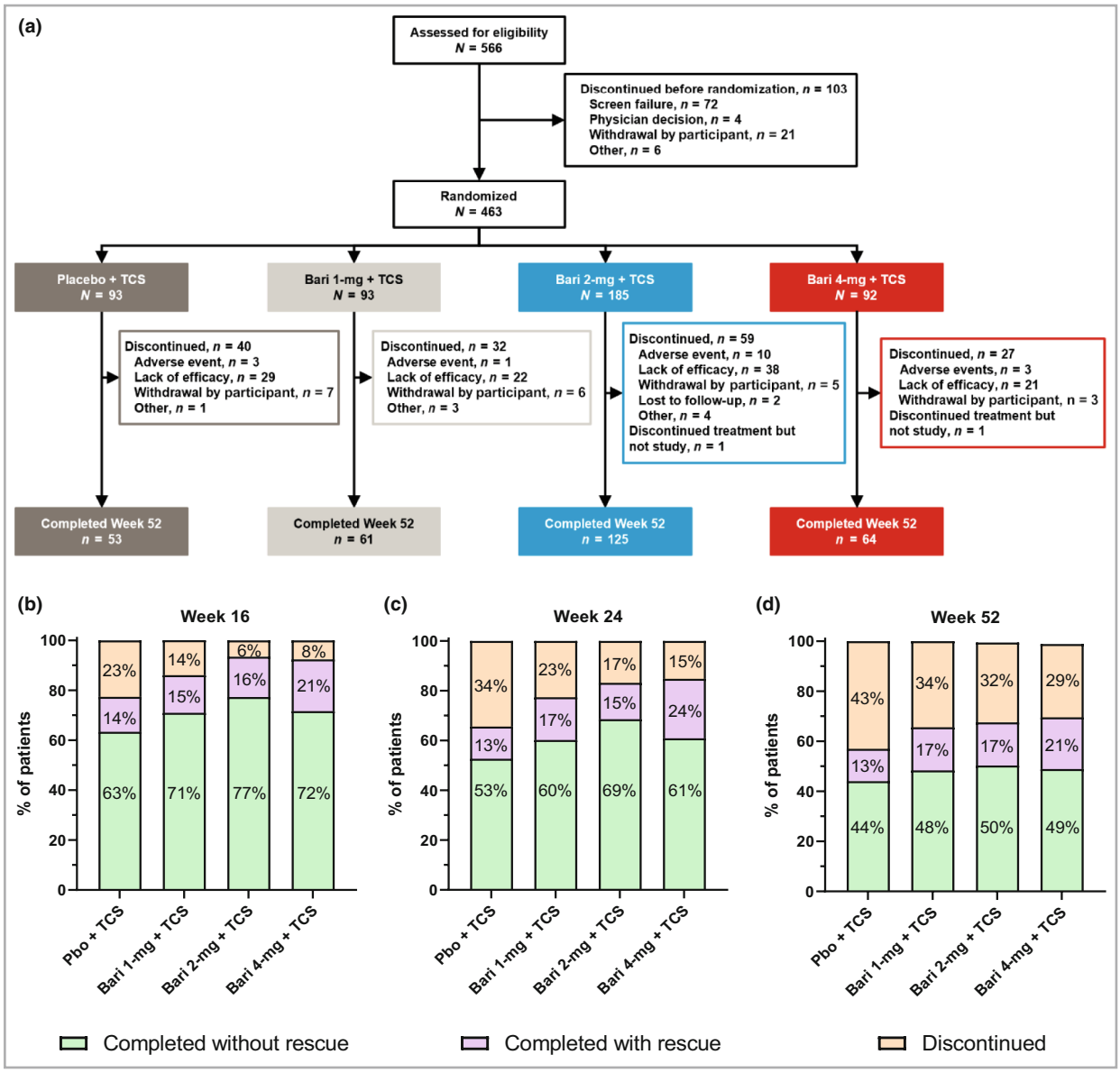

Figure 1 (a) Patient flow diagram through week 52 of BREEZE-AD4. (b–d) Proportions of patients in each treatment group at week 16 (b), 24 (c) and 52 (d) who had either discontinued the study or who had completed the indicated study visit with or without receiving rescue therapy. Bari, baricitinib; Pbo, placebo; TCS, topical corticosteroids

placebo + TCS within the graphical testing procedure for vIGA-AD (0,1) at week 16 but the nominal P-value was 0·03. Subsequent key secondary outcomes were not tested within the graphical testing procedure (Figure S1; see Supporting Information) including vIGA-AD (0,1) and EASI 75 at week 24, the proportion of patients achieving ≥ 75% improvement in the SCORing Atopic Dermatitis Index (SCORAD 75) and EASI 90 at week 16, and Itch NRS ≥ 4-point improvement or ADSS item 2 at week 1; key secondary outcomes for baricitinib 1 mg and 2 mg (+ TCS) were also not tested.

Outside of the graphical testing procedure, significant (nominal $P < 0·05$) improvements vs. placebo + TCS were observed with baricitinib 1 mg and 2 mg (+ TCS) in EASI PCFB at week 16 and Itch NRS ≥ 4-point improvement at weeks 2, 4 and 16; with baricitinib 2 mg + TCS in Skin Pain NRS and SCORAD 75 at week 16; and with baricitinib 4 mg + TCS in ADSS item 2 at week 1.

Additional efficacy analyses

In the baricitinib 2 mg and 4 mg (+ TCS) groups, significantly (nominal $P < 0·05$) greater response was observed at week 16 for the mean CFB in the Patient-Oriented Eczema Measure (POEM) and for the proportion of patients who achieved POEM ≥ 4-point improvement from baseline (primary censoring rule, NRI and MMRM) (Table 2). Baricitinib 4 mg + TCS resulted in significantly (nominal $P < 0·05$) greater responses vs. placebo + TCS at week 16 for the mean

Table 1 Baseline characteristics

	Placebo + TCS, N = 93	Bari 1-mg + TCS, N = 93	Bari 2-mg + TCS, N = 185	Bari 4-mg + TCS, N = 92
Sex, male, n (%)	49 (53)	58 (62)	133 (72)	57 (62)
Age, years	38·7 (13·6)	38·9 (14·0)	37·3 (13·6)	38·7 (13·3)
Race, n (%)				
White	74 (80)	70 (75)	145 (78)	71 (77)
Asian	16 (17)	19 (20)	36 (19)	18 (20)
Weight, kg	74·8 (17·3)	72·2 (15·7)	76·6 (17·4)	77·3 (20·4)
BMI, kg m^{-2}	25·9 (5·4)	25·0 (4·7)	26·0 (5·5)	26·3 (5·7)
Duration since diagnosis, years	27·2 (15·6)	25·1 (15·9)	25·3 (13·7)	27·5 (16·2)
Prior ciclosporin use, n (%)	58 (62)	60 (65)	129 (70)	60 (65)
vIGA-AD[a]	3·5 (0·5)	3·5 (0·5)	3·5 (0·5)	3·5 (0·5)
3, n (%)	43 (46)	46 (49)	91 (49)	45 (49)
4, n (%)	50 (54)	47 (51)	93 (51)	47 (51)
EASI	30·9 (11·6)	34·3 (13·5)	30·6 (12·4)	32·7 (13·7)
SCORAD	69·1 (13·0)	70·9 (14·1)	67·8 (13·4)	68·2 (13·0)
BSA	48·4 (21·3)	56·6 (23·8)	50·1 (22·2)	53·9 (23·8)
POEM, n (%)	21·3 (5·7)	21·4 (6·0)	21·3 (5·9)	20·8 (6·0)
≥ 4	92 (99)	92 (99)	183 (99)	91 (99)
Itch NRS	7·1 (1·9)	6·7 (2·3)	6·7 (1·9)	6·7 (2·3)
≥ 4, n (%)	85 (91)	78 (84)	166 (90)	76 (83)
ADSS item 2	1·6 (1·6)	2·2 (2·7)	1·9 (3·1)	2·1 (1·8)
DLQI	14·5 (6·9)	14·3 (8·3)	13·6 (7·4)	14·0 (8·1)
Skin Pain NRS	6·5 (2·3)	6·3 (2·7)	6·1 (2·4)	6·1 (2·6)

ADSS, Atopic Dermatitis Sleep Scale; Bari, baricitinib; BMI, body mass index; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; NRS, numeric rating scale; POEM, Patient-Oriented Eczema Measure; SCORAD, SCORing Atopic Dermatitis Index; TCS, topical corticosteroids; vIGA-AD, validated Investigator Global Assessment of Atopic Dermatitis. [a]vIGA-AD was scored on a numeric 5-point scale ranging from 0 (clear) to 4 (severe). Unless otherwise specified, values are presented as mean (SD). Percentages are calculated as number of patients in the specified category/number of observed patients in the analysis.

CFB in the Dermatology Life Quality Index (DLQI) and for the proportion of patients who achieved a 0 or 1 score on the DLQI (DLQI 0,1) (primary censoring rule, NRI and MMRM) (Table 2).

Maintenance of efficacy

Efficacy outcomes through week 52 (secondary censoring rule) are presented in Table 3, Figures 2–4 (mLOCF) and Figures S2–S3 (NRI and MMRM) (see Supporting Information). Improvements in the signs and symptoms of AD with baricitinib + TCS persisted through week 52 for both mLOCF and NRI analyses.

EASI 75 and vIGA-AD (0, 1) responses remained numerically similar from week 16 to week 52 for all baricitinib groups (Figure 2a, c). Statistically significant improvements vs. placebo + TCS were maintained for all baricitinib groups through week 52 for EASI PCFB (Figure 2b). Itch NRS ≥ 4-point improvement responses persisted through week 52 with baricitinib 1 mg and 2 mg (+ TCS); responses for baricitinib 4 mg + TCS were 48% at week 16 and 34% at week 52, but statistical significance vs. placebo + TCS was maintained through week 52 (Figure 3a). All baricitinib groups maintained stable levels of improvement in Skin Pain NRS and in ADSS item 2 through week 52 and baricitinib 4 mg + TCS maintained significant improvements vs. placebo + TCS through week 52 (Figure 3b, c). Improvements in POEM and DLQI were numerically greater with baricitinib + TCS than with placebo + TCS through week 52; responses were generally lower at week 52 than week 16 (Figure 4). Significant improvements vs. placebo + TCS at week 52 were observed for mean CFB in POEM (4 mg), POEM ≥ 4-point improvement (4 mg, 2 mg and 1 mg), mean CFB in DLQI (4 mg and 2 mg) and DLQI (0,1) (4 mg).

Patients receiving baricitinib used less background TCS than placebo through week 52, with significant differences observed for baricitinib 1 mg and 2 mg (Table 3). The mean number of days without use of background TCS through week 52 was greater with baricitinib than placebo, but these differences were not statistically significant.

Safety

A higher proportion of patients reported at least one treatment-emergent adverse event (TEAE) in the baricitinib groups vs. placebo (Table 4); most were mild or moderate in severity. Severe TEAEs were most frequent in the placebo and baricitinib 1-mg groups. The most common TEAEs in the baricitinib 4-mg group were nasopharyngitis (37·0%), herpes simplex (15·2%), influenza (15·2%) and headache (10·9%).

Table 2 Efficacy endpoints through week 24 (primary censoring rule, NRI and MMRM)

	PBO + TCS (N = 93)	Bari 1-mg + TCS (N = 93)			Bari 2-mg + TCS (N = 185)			Bari 4-mg + TCS (N = 92)		
	Response	Response	Difference vs. PBO (95% CI)	P-value vs. PBO	Response	Difference vs. PBO (95% CI)	P-value vs. PBO	Response	Difference vs. PBO (95% CI)	P-value vs. PBO
Primary endpoint										
EASI 75										
Week 16	16 (17%)	–	–	–	51 (28%)	10·4% (−0·4 to 19·7)	0·071	29 (32%)	14·3% (1·9 to 26·2)	0·031[a]
Key secondary endpoints										
EASI 75										
Week 16	16 (17%)	21 (23%)	5·4% (−6·2 to 16·8)	0·427	–	–	–	–	–	–
Week 24	16 (17%)	28 (30%)	12·9% (0·7 to 24·7)	0·058	51 (28%)	10·4% (−0·4 to 19·7%)	0·072	23 (25%)	7·8% (−4·0 to 19·4)	0·224
EASI 90										
Week 16	6 (7%)	8 (9%)	2·2% (−5·9 to 10·4)	0·611	19 (10%)	3·8% (−4·0 to 10·1)	0·325	13 (14%)	7·7% (−1·3 to 16·9)	0·100
EASI, LS mean (SE) PCFB										
Week 16	−42·69 (4·135)	−60·34 (4·018)	−17·65 (−28·71 to −6·58)	0·002	−56·05 (2·755)	−13·35 (−22·83 to −3·87)	0·006	−63·31 (3·922)	−20·62 (−31·54 to −9·70)	< 0·001[a]
Itch NRS ≥4-point improvement[b]										
Week 1	1 (1%)	3 (4%)	2·7% (−3·1to 9·6)	0·294	7 (4%)	3·0% (−2·6 to 7·4)	0·163	6 (8%)	6·7% (0.0 to 15·1)	0·067
Week 2	4 (5%)	11 (14%)	9·4% (0·3 to 19·2)	0·043	23 (14%)	9·1% (1·0 to 15·9)	0·017	17 (22%)	17·7% (7·2 to 28·6)	0·002[a]
Week 4	7 (8%)	15 (19%)	11·0% (0·4 to 21·9)	0·043	40 (24%)	15·9% (6·1to 24·1)	0·001	31 (41%)	32·6% (19·6 to 44·5)	< 0·001[a]
Week 16	7 (8%)	18 (23%)	14·8% (3·7 to 26·1)	0·012	38 (23%)	14·7% (5·0 to 22·8)	0·002	29 (38%)	29·9% (17·2 to 41·9)	< 0·001[a]
Skin Pain NRS, LS mean (SE) CFB										
Week 16	−1·56 (0·284)	−2·27 (0·274)	−0·70 (−1·47 to 0·06)	0·071	−2·40 (0·193)	−0·84 (−1·50 to −0·17)	0·013	−3·02 (0·271)	−1·45 (−2·21 to −0·69)	< 0·001[a]
ADSS item 2, LS mean (SE) CFB										
Week 1	−0·48 (0·097)	−0·54 (0·096)	−0·06 (−0·32 to 0·20)	0·645	−0·62 (0·071)	−0·14 (−0·37 to 0·09)	0·226	−0·82 (0·100)	−0·34 (−0·61 to −0·08)	0·011
Week 16	−0·63 (0·149)	−1·05 (0·142)	−0·42 (−0·82 to −0·02)	0·039	−0·85 (0·099)	−0·21 (−0·56 to 0·13)	0·229	−1·42 (0·140)	−0·79 (−1·18 to −0·39)	< 0·001[a]
vIGA-AD (0,1)[c]										
Week 16	9 (10%)	12 (13%)	3·2 (−6·2 to 12·7)	0·513	28 (15%)	5·5% (−3·4 to 12·9)	0·242	20 (22%)	12·1% (1·5 to 22·5)	0·030
Week 24	12 (13%)	19 (20%)	7·5% (−3·3 to 18·3)	0·183	35 (19%)	6·0% (−3·7 to 14·3)	0·235	12 (13%)	0·1% (−9·8 to 10·1)	0·991

(continued)

Table 2 (continued)

	PBO + TCS (N = 93)	Bari 1-mg + TCS (N = 93)			Bari 2-mg + TCS (N = 185)			Bari 4-mg + TCS (N = 92)		
	Response	Response	Difference vs. PBO (95% CI)	P-value vs. PBO	Response	Difference vs. PBO (95% CI)	P-value vs. PBO	Response	Difference vs. PBO (95% CI)	P-value vs. PBO
SCORAD 75										
Week 16	1 (1%)	6 (6%)	5·4% (−0·5 to 12·3)	0·115	15 (8%)	7·0% (1·3 to 12·0)	0·037	6 (7%)	5·4% (−0·5 to 12·5%)	0·083
Other secondary endpoints										
Itch NRS, LS mean (SE) CFB										
Week 16	−1·42 (0·274)	−2·34 (0·264)	−0·92 (−1·65 to −0·18)	0·015	−2·27 (0·184)	−0·84 (−1·48 to −0·21)	0·010	−2·84 (0·261)	−1·42 (−2·15 to −0·68)	< 0·001
POEM, LS mean (SE) CFB										
Week 16	−4·18 (0·907)	−6·24 (0·872)	−2·06 (−4·47 to 0·36)	0·095	−7·27 (0·602)	−3·09 (−5·16 to −1·01)	0·004	−9·27 (0·855)	−5·09 (−7·48 to −2·70)	< 0·001
DLQI, LS mean (SE) CFB										
Week 16	−4·95 (0·752)	−6·18 (0·719)	−1·23 (−3·23 to 0·77)	0·228	−6·57 (0·494)	−1·62 (−3·35 to 0·10)	0·065	−7·95 (0·705)	−3·01 (−4·99 to −1·02)	0·003
Exploratory endpoints										
POEM ≥4-point improvement										
Week 16	31 (34%)	40 (43%)	9·8% (−4·2 to 23·3)	0·189	101 (55%)	21·5% (9·0–32·8)	0.001	52 (57%)	23·4% (9·0 to 36·5)	0·002
DLQI (0,1)										
Week 16	9 (10%)	12 (13%)	3·2% (−6·2 to 12·7)	0·635	33 (18%)	8·2% (−0·9 to 15·8)	0·141	27 (29%)	19·7% (8·3 to 30·6)	0·002

ADSS, Atopic Dermatitis Sleep Scale; Bari, baricitinib; CFB, change from baseline; CI, confidence interval; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; LS, least square; NRS, Numeric Rating Scale; PBO, placebo; PCFB, percent change from baseline; POEM, Patient-Oriented Eczema Measure; SCORAD, SCORing Atopic Dermatitis Index; SE, standard error; TCS, topical corticosteroid; vIGA-AD, validated Investigator Global Assessment for Atopic Dermatitis. [a]Achieved statistical significance in graphical testing scheme. [b]Assessed for patients with Itch NRS ≥ 4 at baseline. [c]vIGA-AD was scored on a numeric 5-point scale ranging from 0 (clear) to 4 (severe). Unless otherwise indicated, values are presented as n (%). All P-values are nominal.

Table 3 Efficacy outcomes at week 52 of BREEZE-AD4

	PBO + TCS (N = 93)	Bari 1-mg + TCS (N = 93)			Bari 2-mg + TCS (N = 185)			Bari 4-mg + TCS (N = 92)		
	Response	Response	Difference vs. PBO (95% CI)	P-value vs. PBO	Response	Difference vs. PBO (95% CI)	P-value vs PBO	Response	Difference vs. PBO (95% CI)	P- value vs. PBO
EASI 75	25 (27%)	31 (33%)	6·5% (−6·7 to 19·3)	0·382	56 (30%)	3·4% (−8·2 to 14·0)	0·638	34 (37%)	10·1% (−3·3 to 23·0)	0·169
EASI, mean (SE) PCFB	−42·58 (4·140)	−57·82 (4·168)	−15·24 (−26·12 to −4·36)	0·006	−56·36 (3·078)	−13·78 (−23·18 to −4·37)	0·004	−58·35 (4·146)	−15·76 (−26·62 to −4·91)	0·005
vIGA-AD (0,1)[b]	15 (16%)	19 (20%)	4·3% (−6·9 to 15·4)	0·461	33 (18%)	1·7% (−8·3 to 10·4)	0·768	21 (23%)	6·7% (−4·8 to 18·0)	0·255
Itch NRS, mean (SE) CFB	−1·55 (0·267)	−2·43 (0·268)	−0·87 (−1·57 to −0·17)	0·014	−2·16 (0·199)	−0·61 (−1·22 to −0·00)	0·049	−2·78 (0·269)	−1·22 (−1·92 to −0·52)	<0·001
Itch NRS ≥ 4-point improvement[a]	16 (19%)	24 (31%)	11·9% (−1·3 to 24·9)	0·082	38 (23%)	4·1% (−7·1 to 13·9)	0·255	26 (34%)	14·9% (1·4 to 28·0)	0·037
Skin Pain NRS, mean (SE) CFB	−1·85 (0·279)	−2·56 (0·280)	−0·70 (−1·43 to 0·03)	0·059	−2·43 (0·208)	−0·58 (−1·21 to 0·05)	0·073	−2·96 (0·281)	−1·10 (−1·83 to −0·37)	0·003
ADSS item 2, mean (SE) CFB	−0·44 (0·112)	−0·59 (0·120)	−0·15 (−0·44 to 0·15)	0·329	−0·61 (0·089)	−0·16 (−0·41 to 0·09)	0·204	−0·67 (0·114)	−0·22 (−0·51 to 0·07)	0·129
POEM, mean (SE) CFB	−4·40 (0·837)	−5·94 (0·831)	−1·54 (−3·72 to 0·64)	0·167	−6·11 (0·621)	−1·70 (−3·60 to 0·20)	0·079	−7·11 (0·834)	−2·71 (−4·89 to −0·52)	0·016
POEM ≥4-point improvement	39 (42%)	54 (59%)	16·3% (1·9 to 29·8)	0·030	106 (58%)	15·5% (3·0 to 27·4)	0·016	54 (59%)	16·3% (1·9 to 29·8)	0·020
DLQI, mean (SE) CFB	−4·76 (0·716)	−6·41 (0·711)	−1·65 (−3·52 to 0·22)	0·083	−6·79 (0·532)	−2·03 (−3·65 to −0·40)	0·015	−7·02 (0·714)	−2·26 (−4·14 to −0·39)	0·018
DLQI (0,1)	10 (11%)	14 (15%)	4·3% (−5·6 to 14·2)	0·465	32 (17%)	6·5% (−2·7 to 14·3)	0·241	25 (27%)	2·91% (1·30 to 6·52)	0·009
Quantity of background TCS used from week 0 to 52, mean (SE), grams[c]	742·74 (81·32)	522·56 (81·29)	−220·18 (−427·93 to −12·44)	0·038	544·99 (61·04)	−197·75 (−377·55 to −17·94)	0·031	583·94 (80·79)	−158·80 (−366·17 to 48·56)	0·133
Mean (SE) number of days without use of background TCS from week 0 to 52[d]	35·13 (10·25)	59·86 (10·26)	24·73 (−2·07 to 51·54)	0·070	50·77 (7·66)	15·64 (−7·61 to 38·90)	0·187	58·15 (10·30)	23·02 (−3·86 to 49·89)	0·093

ADSS, Atopic Dermatitis Sleep Scale; Bari, baricitinib; CFB, change from baseline; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; mLOCF, modified last observation carried forward; NRS, Numeric Rating Scale; PBO, placebo; PCFB, percent change from baseline; POEM, Patient-Oriented Eczema Measure; SCORAD, SCORing Atopic Dermatitis Index; SE, standard error; TCS, topical corticosteroids; vIGA-AD, validated Investigator Global Assessment for Atopic Dermatitis. [a]Assessed for patients with Itch NRS ≥ 4 at baseline. [b]vIGA-AD was scored on a numeric 5-point scale ranging from 0 (clear) to 4 (severe). [c]Analyses were conducted using the primary censoring rule, which assumes that after first rescue therapy date or permanent study drug discontinuation, patients use the same amount of TCS as they did before. [d]Analyses were conducted using the primary censoring rule, which assumes that after the first rescue therapy date or permanent study drug discontinuation, background TCS is applied each day. Except where specified, data represent analysis using the secondary censoring rule and mLOCF. Unless otherwise indicated, values are presented as n (%). All P-values are nominal.

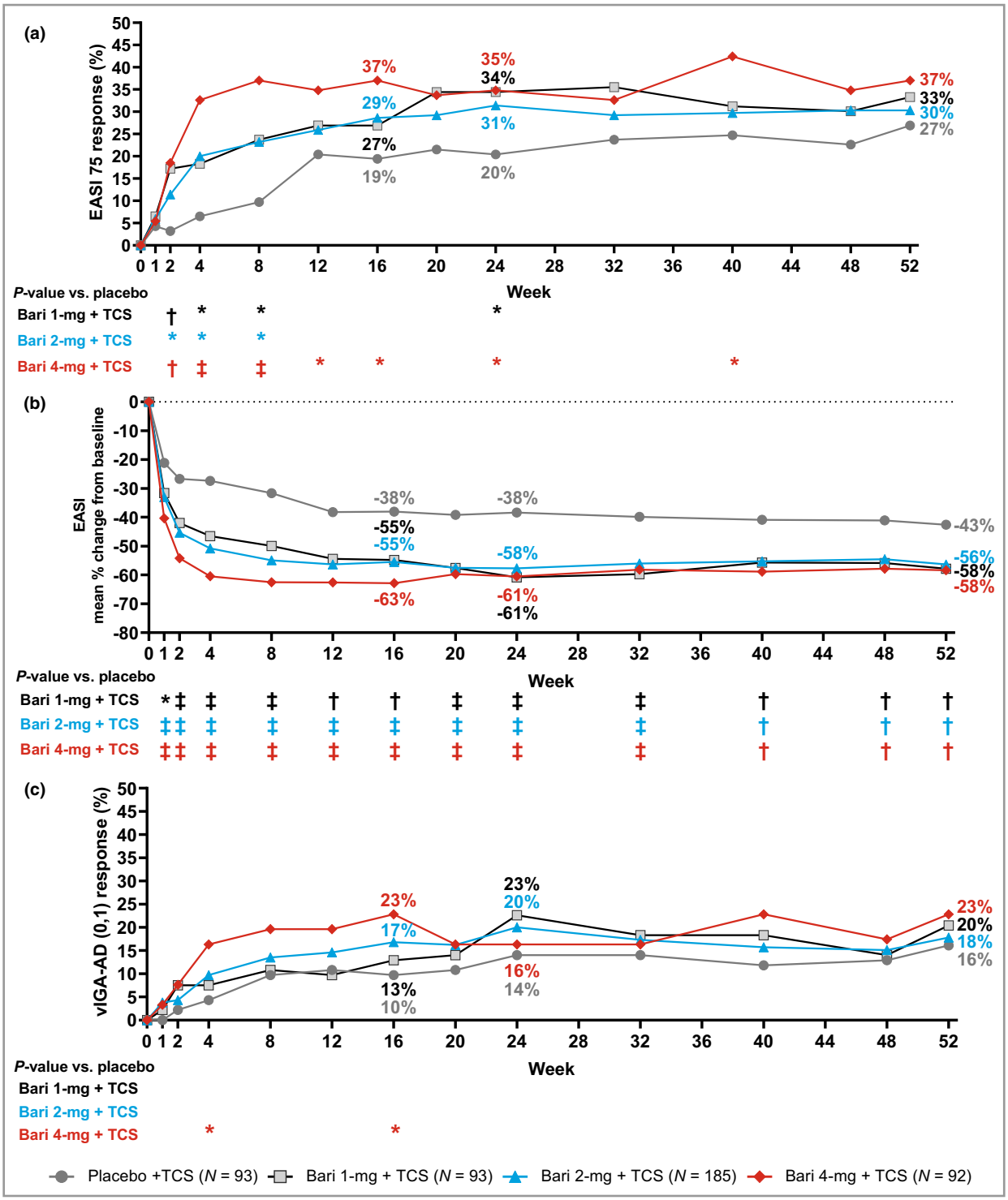

Figure 2 Proportion of patients achieving a 75% improvement from baseline in EASI (a), the mean percent change from baseline in EASI (b), and the proportion of patients achieving a score of clear (0) or almost clear (1) with ≥ 2-point improvement from baseline in vIGA-AD (c) through week 52 of BREEZE-AD4. Results are presented using the secondary censoring rule where observations were censored after permanent study drug discontinuation. Missing data were handled using modified last observation carried forward. Bari + TCS vs. placebo + TCS P-values (nominal): *P < 0·05, †P < 0·01, ‡P < 0·001. Bari, baricitinib; EASI, Eczema Area and Severity Index; TCS, topical corticosteroids; vIGA-AD, validated Investigator's Assessment of Atopic Dermatitis

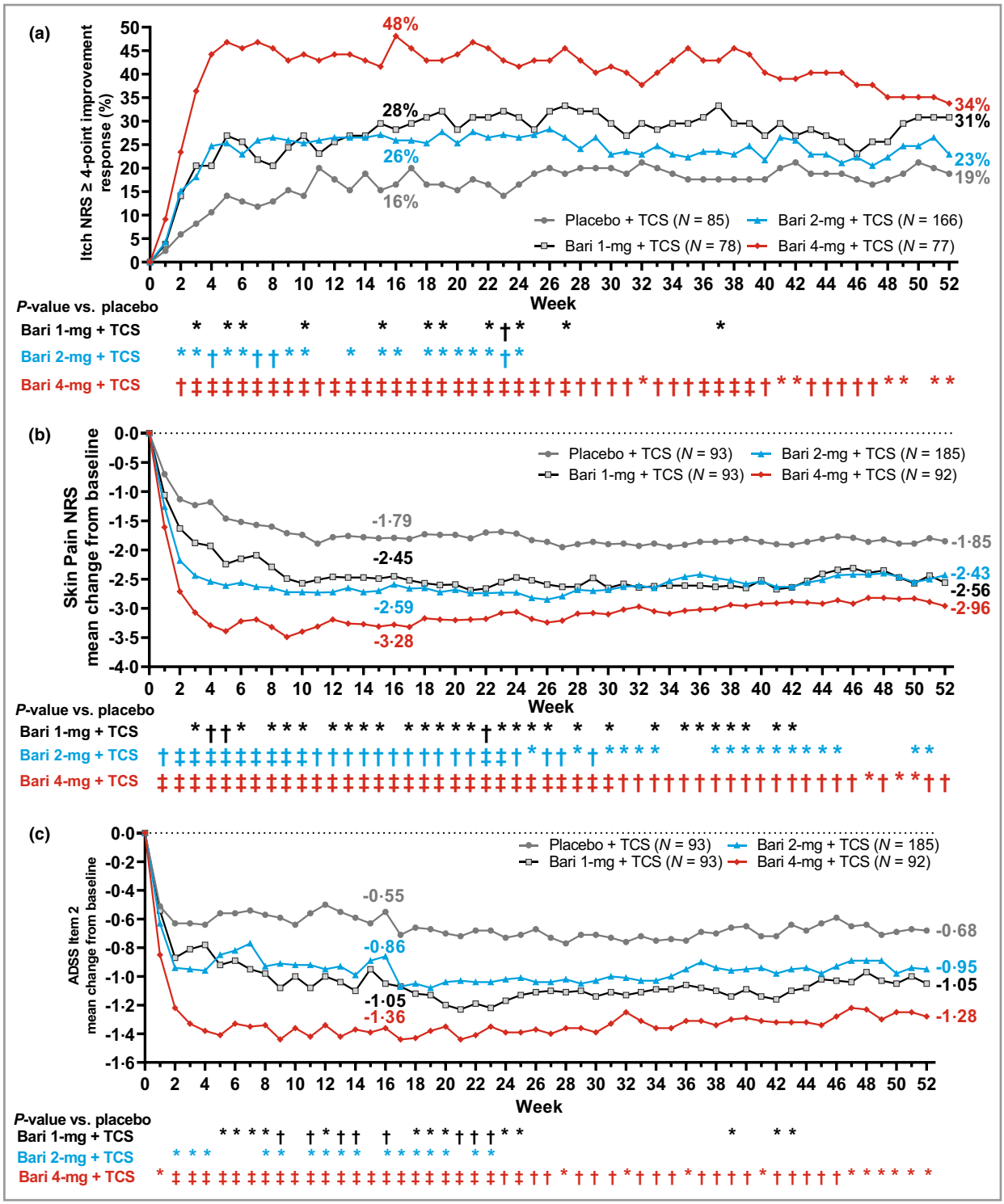

Figure 3 Proportion of patients achieving Itch NRS ≥ 4-point improvement from baseline (a), mean change from baseline in Skin Pain NRS (b), and mean change from baseline in ADSS item 2 (number of night-time awakenings due to itch) (c). Results are presented using the secondary censoring rule where observations were only censored after permanent study drug discontinuation. Missing data were handled using modified last observation carried forward. Bari + TCS vs. placebo + TCS P-values (nominal): *P < 0·05, †P < 0·01, ‡P < 0·001. ADSS, Atopic Dermatitis Sleep Scale; Bari, baricitinib; NRS, Numeric Rating Scale

Serious AEs (SAEs) were most frequent in the baricitinib 1-mg and 4-mg groups. Most SAEs were reported by only one patient for each type of SAE and the most common SAE was AD; bursitis was reported by two patients in the baricitinib 1-mg group (Table S3; see Supporting Information). Discontinuation owing to an AE was most common in the baricitinib 2-

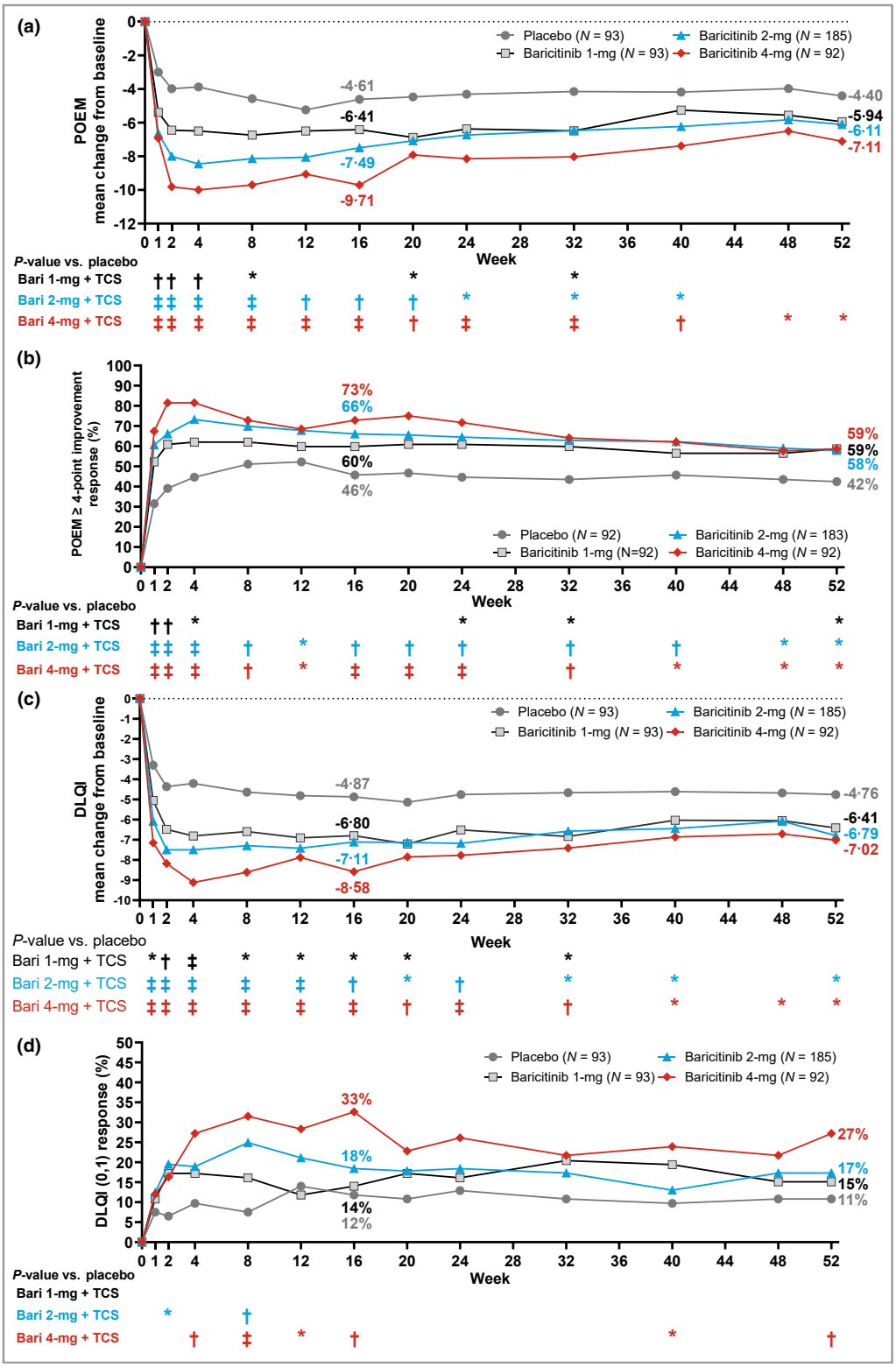

Figure 4 Mean change from baseline in POEM (a), the proportion of patients achieving at least a 4-point improvement in the POEM (b), mean change from baseline in DLQI (c), and the proportion of patients achieving 0 or 1 in DLQI (d). Results are presented using the secondary censoring rule where observations were only censored after permanent study drug discontinuation. Missing data were handled using modified last observation carried forward. Bari + TCS vs. placebo + TCS P-values (nominal): *P < 0·05, †P < 0·01, ‡P < 0·001. Bari, baricitinib; DLQI, Dermatology Life Quality Index; POEM, Patient-Oriented Eczema Measure

Table 4 Summary of safety through week 52 in BREEZE-AD4

	PBO (N = 93)	Bari 1-mg (N = 93)	Bari 2-mg (N = 185)	Bari 4-mg (N = 92)
Treatment-emergent adverse events	62 (66·7)	68 (73·1)	149 (81·0)	82 (89·1)
Mild	33 (35·5)	29 (31·2)	72 (39·1)	38 (41·3)
Moderate	21 (22·6)	31 (33·3)	65 (35·3)	37 (40·2)
Severe	8 (8·6)	8 (8·6)	12 (6·5)	7 (7·6)
Serious adverse events	5 (5·4)	7 (7·5)	9 (4·9)	10 (10·9)
Discontinuation from study treatment owing to adverse event	2 (2·2)	1 (1·1)	10 (5·4)	3 (3·3)
Death	0	0	0	0
Major adverse cardiovascular events (adjudicated)	0	0	1 (0·5)	0
Common treatment-emergent adverse events[a]				
Nasopharyngitis	14 (15·1)	16 (17·2)	38 (20·7)	34 (37·0)
Herpes simplex[b]	7 (7·5)	7 (7·5)	17 (9·2)	14 (15·2)
Influenza	2 (2·2)	3 (3·2)	14 (7·6)	14 (15·2)
Headache	8 (8·6)	8 (8·6)	14 (7·6)	10 (10·9)
Back pain	5 (5·4)	6 (6·5)	6 (3·3)	6 (6·5)
Diarrhoea	3 (3·2)	2 (2·2)	9 (4·9)	6 (6·5)
Upper abdominal pain	3 (3·2)	2 (2·2)	7 (3·8)	5 (5·4)
Conjunctivitis	1 (1·1)	1 (1·1)	3 (1·6)	5 (5·4)
Erysipelas	1 (1·1)	0	4 (2·2)	5 (5·4)
Urinary tract infection	0	1 (1·1)	5 (2·7)	5 (5·4)
CPK elevation[c]	16 (17·6)	21 (22·8)	47 (25·7)	27 (29·3)
Increase to grade ≥ 3	2 (2·2)	4 (4·3)	5 (2·8)	2 (2·2)
Treatment-emergent infections	37 (39·8)	52 (55·9)	110 (59·8)	67 (72·8)
Opportunistic infections	0	0	2 (1·1)	1 (1·1)
Herpes zoster	0	4 (4·3)	6 (3·3)	3 (3·3)
Serious infections	2 (2·2)	2 (2·2)	5 (2·7)	4 (4·3)
Tuberculosis	0	0	0	0
Skin infections requiring antibiotic treatment	8 (8·6)	12 (12·9)	24 (13·0)	10 (10·9)
Adverse events of special interest				
Deep vein thrombosis	0	0	0	0
Pulmonary embolism	0	0	0	0
Gastrointestinal perforations	0	0	0	0
NMSC	1 (1·1)	0	1 (0·5)	0
Malignancies other than NMSC	1 (1·1)	0	0	0

Bari, baricitinib; CPK, creatine phosphokinase; CTCAE, Common Terminology for Adverse Events. NMSC, nonmelanoma skin cancer; PBO, placebo. Data are presented as n (%). [a]Common treatment-emergent adverse events are defined as events occurring in ≥ 5% of patients in the baricitinib 4 mg + TCS treatment group. [b]Includes preferred terms of oral herpes, herpes simplex, eczema herpeticum, genital herpes simplex, genital herpes, and Kaposi varicelliform eruption as defined in the medical dictionary for regulatory activities.

mg group (5·4%) (Table S4; see Supporting Information). No deaths occurred.

The proportion of patients with at least one treatment-emergent infection was higher in the baricitinib groups than in the placebo group. Herpes simplex and herpes zoster were most frequent in the baricitinib 4-mg and baricitinib 1-mg groups, respectively. Skin infections requiring antibiotic treatment were most frequent in the baricitinib 2-mg and 1-mg groups. Opportunistic infections were reported in two (1·1%) patients receiving baricitinib 2 mg (one event each of multidermatomal herpes zoster and ophthalmic herpes) and in one (1·1%) patient receiving baricitinib 4 mg (multidermatomal herpes zoster).

One major adverse cardiovascular event was reported in the baricitinib 2-mg treatment group (SAE, adjudicated as acute myocardial infarction). Risk factors included age, history of smoking and hypertension, and the investigator did not consider the event to be related to the study drug. Two events of nonmelanoma skin cancer were reported, i.e. one event of Bowen disease (placebo) and one event of basal cell carcinoma (baricitinib 2 mg). One event of breast cancer was reported in the placebo group. There were no reports of tuberculosis, deep vein thrombosis, pulmonary embolism or gastrointestinal perforation.

Elevations in creatine phosphokinase (CPK) were observed more frequently in patients receiving baricitinib than placebo. Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or 4 CPK elevations occurred in < 5% of patients in all treatment groups and were most common in the baricitinib 1-mg group. One event of myalgia (baricitinib 2 mg) was associated with elevated CPK (6028 U L^{-1}) but was considered to be due to strenuous exercise. Two patients (one each in baricitinib 2 mg and 4 mg) had slightly elevated CPK levels (338–558 U L^{-1}) at the time of muscle-related events.

Haematological elevations to CTCAE grade 3 were infrequent and no elevations to grade 4 were reported (Table S5; see Supporting Information). Increased lipid levels including low- and high-density lipoproteins were observed in the baricitinib treatment groups. No meaningful differences in liver enzyme changes were observed between treatment groups. Additional changes in laboratory analytes are summarized in Table S5.

Discussion

BREEZE-AD4 is the first study to evaluate the efficacy and safety of baricitinib + TCS in patients with moderate-to-severe AD who had inadequate response, intolerance or contraindication to CA. At week 16, baricitinib 4 mg + TCS was superior to placebo + TCS in improving multiple domains of AD including skin inflammation (EASI 75 and EASI PCFB), pruritus (Itch NRS), skin pain (Skin Pain NRS), and sleep disturbance owing to itch (ADSS item 2). Pruritus, a key and problematic symptom of AD, showed rapid and significant improvements within 2 weeks of treatment with baricitinib 4 mg.[17] Baricitinib 1 mg and 2 mg (+ TCS) did not achieve superiority to placebo + TCS for the primary or key secondary endpoints, but significant improvements were observed outside of the graphical testing procedure. Significant improvements vs. placebo + TCS were observed at week 16 in non-gated endpoints of POEM for patients receiving baricitinib 2 mg and 4 mg (+ TCS) and DLQI for patients receiving 4 mg + TCS. Responses at week 16 were generally maintained through 52 weeks of treatment. In the baricitinib 4 mg + TCS group, fewer patients achieved Itch NRS ≥ 4-point improvement at week 52 than at week 16, but responses remained statistically significant vs. placebo + TCS.

Owing to the flaring nature of AD, it was expected that the number of patients who used higher-potency TCS at some point would increase over time. The proportion of patients requiring rescue therapy was lower with placebo + TCS vs. baricitinib + TCS, but the placebo + TCS group had the highest discontinuation rate throughout the trial period. Overall, discontinuation rates by week 52 were high across groups, which may be linked to the long duration of the placebo-controlled period, as comparable rates were observed in a previous trial of similar design. Discontinuation rates were lower in the baricitinib + TCS groups in a dose-dependent manner. This may be linked to an overall better control of disease manifestations illustrated by the higher response levels with the 4-mg dose on subjective symptoms of skin discomfort (e.g. pain and itch).

More patients reported TEAEs with baricitinib than with placebo but most were not severe or serious and there was no relationship with dose observed for severe or serious events. Most SAEs were reported only once and the most frequent SAE reported was AD. Common TEAEs included nasopharyngitis, herpes simplex, influenza and headache. Two events of nonmelanoma skin cancer (one placebo and one baricitinib 2 mg) and one event of breast cancer (placebo) were reported. One major adverse cardiovascular event (myocardial infarction) was reported in the baricitinib 2-mg group. As in other studies of baricitinib and other JAK inhibitors, CPK elevations were more frequent in patients receiving baricitinib than placebo, but grade 3 or 4 CPK elevations were uncommon (< 5%) and did not exhibit a relationship with dose.[14,18,19] No deaths and no AEs of tuberculosis, deep vein thrombosis, pulmonary embolism or gastrointestinal perforations were reported. The safety profile was consistent with the known safety findings of baricitinib in AD.[14–16]

Few conventional systemic therapies are approved for AD and they often have contraindications or safety concerns that limit their use.[8–10] Dupilumab is the first approved biological systemic therapy for AD and provided clinical benefit both as a monotherapy and in combination with TCS, but not all patients achieve sufficient clinical improvement with dupilumab.[10,12,13] For example, approximately 40% of patients did not achieve EASI 75 in a phase III clinical study of dupilumab with background TCS in patients with inadequate response or intolerance to CA, or for whom CA was medically inadvisable.[20] Biological agents also may not provide the flexibility or convenience of use that is sometimes required in the management of AD.

Baricitinib is an oral therapy approved for moderate-to-severe AD in adult patients who are candidates for systemic therapy. In prior studies, baricitinib was efficacious in treating moderate-to-severe AD both as a monotherapy and with background TCS.[14,15] BREEZE-AD4 expands on these studies by enrolling a patient population who had inadequate response, intolerance or contraindication to CA. About two-thirds of the patients reported prior use of CA. These patients may be more difficult to treat owing to the chronic, severe and/or refractory nature of their disease, which may explain why overall response rates in BREEZE-AD4 were lower than in the previously reported BREEZE-AD7 combination therapy trial.[8–10,21]

Strengths of BREEZE-AD4 include enrolment of a clinically relevant patient population and inclusion of background TCS use in all treatment arms, consistent with clinical practice. Allowing background TCS and an option for rescue therapy mitigated ethical concerns about including a long-term (52-week) double-blind treatment period with a placebo comparator. However, the elevated use of background TCS in the placebo group compared with the baricitinib treatment group may have been responsible for the higher than anticipated placebo response, which led to a decrease in the power of the trial.

At week 16, baricitinib 4 mg + TCS was superior to placebo + TCS for treatment of the signs and symptoms of moderate-to-severe AD. Improvements were rapidly achieved with baricitinib + TCS and responses were maintained through 52 weeks of treatment. The safety profile of baricitinib was consistent with previous studies in patients with moderate-to-severe AD. Thus, baricitinib may be an additional therapeutic option for patients with moderate-to-severe AD, including patients with inadequate response, intolerance or contraindication to CA.

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Conflicts of interest

T.B. is/has been a lecturer and/or consultant for the following companies: AbbVie, Allmiral, AnaptysBio, Arena, Asana Biosciences, Bayer Health, BioVerSys, Boehringer Ingelheim, Bristol Myers Squibb, Dermavant/Roivant, DermTreat, Domain Therapeutics, DS Pharma, Eli Lilly and Company, RAPT/FLX Bio, Galapagos/MorphoSys, Galderma, Glenmark, GSK, Incyte, Janssen, Kirin, Kymab, LEO, LG Chem, L'Oréal, Novartis, Numab, OMPharma, Pfizer, Pierre Fabre, Sanofi/Regeneron and UCB. T.B. is founder of the nonprofit biotech company 'Davos Biosciences' within the International Kühne-Foundation. K.R. has served as an advisor, and/or paid speaker for, and/or participated in clinical trials sponsored by: AbbVie, Almirall, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Forward Pharma, Gilead, Galderma, Janssen-Cilag, Kyowa Kirin, Leo, Eli Lilly and Company, Medac, Novartis, Ocean Pharma, Pfizer, Sanofi and UCB; K.R. is cofounder of Moonlake Immunotherapeutics. C.P. has been a consultant for Almirall, Amgen, AbbVie, Boehringer Ingelheim, Celgene, Galderma, Eli Lilly and Company, Novartis, Janssen, Sandoz, Pierre Fabre, Pfizer, Leo Pharma, Medac, Merck, Regeneron, Sanofi and UCB Pharma. Y.T. has received fees for lectures from Mitsubishi Tanabe Pharma Corporation, Taiho Pharmaceutical Co., Ltd., Sanofi K.K., Maruho Co., Ltd., Torii Pharmaceutical Co., Ltd. and Novartis Pharma K.K. M.A. has been an advisory board member, consultant, received grants, received research support, been an investigator, and/or received honoraria as a speaker from AbbVie, Almirall, Amgen, Biogen, Boehringer Ingelheim, Celgene, Centocor, Eli Lilly and Company, GSK, Hexal, Janssen-Cilag, LEO Pharma, Medac, Merck, MSD, Mundipharma, Novartis, Pfizer, Sandoz, UCB Biosciences Inc. and Xenoport. J.P.L. received grants and consulting fees from AbbVie, Amgen, Boehringer Ingelheim, Celgene, Eli Lilly and Company, Galderma International, Janssen, LEO Pharma, Merck, Novartis, Pfizer, Pierre Fabre and Sanofi. P.D.G. has received speaker's fees from, and/or been an investigator for, and/or has participated in advisory boards for Wyeth/Pfizer, Schering-Plough/MSD, Abbott/AbbVie, Janssen-Cilag, Merck-Serono, Leo, Novartis, UCB, Amgen, Celgene, Eli Lilly and Company, Galderma, BMS, Meda, Maruho, Flen, Menarini, Almirall, PellePharm and Mylan. Y.D., R.L., D.B., A.M.D.L., E.M. and J.M.J. are employees of, and own stock in, Eli Lilly and Company. K.E. has received speaker's fees from, and/or has been a member of advisory boards for AbbVie, Almirall, Boehringer Ingelheim, BMS, Hexal, Leo, Eli Lilly and Company, Janssen, Pfizer, Novartis, Sanofi and UCB.

Data availability

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, 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 www.vivli.org.

Ethics statement

BREEZE-AD4 (ClinicalTrials.gov: NCT03428100) was conducted in accordance with the ethical principles of the Declaration of Helsinki. The study was approved by the ethical review board at each participating site. Study participants provided written informed consent prior to performing study procedures.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Appendix S1 Supplementary methods and patient information.

Figure S1 Illustration of graphical multiple-testing procedure for BREEZE-AD4.

Figure S2 Proportion of patients achieving a 75% improvement from baseline in Eczema Area and Severity Index (EASI) (a), the mean percentage change from baseline in EASI (b), and the proportion of patients achieving a score of clear (0) or almost clear (1) with ≥2-point improvement from baseline in validated Investigator Global Assessment of Atopic Dermatitis (c) through week 52 of BREEZE-AD4.

Figure S3 Proportion of patients achieving Itch Numeric Rating Scale (NRS) ≥ 4-point improvement from baseline (a),

mean change from baseline in Skin Pain NRS (b), and mean change from baseline in Atopic Dermatitis Sleep Scale item 2 (number of night-time awakenings due to itch) (c).

Table S1 BREEZE-AD4 efficacy endpoints.

Table S2 Prior ciclosporin history at baseline.

Table S3 Serious adverse events through week 52 of BREEZE-AD4.

Table S4 Adverse events leading to permanent discontinuation at week 52.

Table S5 Important changes in laboratory analytes.

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