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Baricitinib in Patients with Moderate-to-Severe Atopic Dermatitis and Inadequate Response to Topical Corticosteroids: Results from Two Randomised Monotherapy Phase 3 Trials

Running title: Baricitinib Atopic Dermatitis Phase 3 Results

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Capsule Summary (67/70 words):

For original articles please answer the following new statements in 2 or 3 bulleted statements (limit of 70 words): What's already known about this topic? What does this study add?

- Atopic dermatitis (AD) is a chronic, heterogeneous inflammatory skin disease with few approved therapies for patients with moderate-to-severe disease.
- These two Phase 3 trials show that baricitinib, an oral inhibitor of Janus kinase 1 and 2, significantly improved clinical signs and symptoms of AD compared to placebo within the first 16 weeks of treatment.
- Baricitinib may represent a first-in-class oral treatment option for adult patients with moderate-to-severe AD.

SUMMARY (250/250 words)

Background: Baricitinib, an oral selective Janus kinase 1 and 2 inhibitor, effectively reduced atopic dermatitis (AD) severity in a Phase 2 study with concomitant topical corticosteroids.

Objectives: To evaluate the efficacy and safety of baricitinib in patients with moderate-to-severe AD and an inadequate response to topical therapies.

Methods: In two independent, multicentre, double-blind, Phase 3 monotherapy trials, BREEZE-AD1 and BREEZE-AD2, adults with moderate-to-severe AD were randomised 2:1:1:1 to once-daily placebo, baricitinib 1-mg, 2-mg or 4-mg for 16 weeks.

Results: At Week 16, more patients achieved the primary endpoint of Validated Investigator's Global Assessment of AD (0, 1) on baricitinib 4-mg and 2-mg compared with placebo in BREEZE-AD1 (N=624; 4-mg 16.8%, 2-mg 11.4%, 1-mg 11.8%, placebo 4.8%; $P<0.001$, $P<0.05$, $P<0.05$), and BREEZE-AD2 (N=615; 4-mg 13.8%, 2-mg 10.6%, 1-mg 8.8%, placebo 4.5%; $P=0.001$, $P<0.05$, $P=0.085$). Improvement in itch was achieved as early as Week 1 for 4-mg and Week 2 for 2-mg. Improvements in night-time awakenings, skin pain, and quality-of-life measures were observed by Week 1 for both 4-mg and 2-mg ($P\leq 0.05$, all comparisons). The most common adverse events in baricitinib-treated patients were nasopharyngitis and headache. No cardiovascular events, venous thromboembolism, gastrointestinal perforation, significant haematological changes, or death were observed with any baricitinib dose.

Conclusions: Baricitinib improved clinical signs and symptoms in patients with moderate-to-severe AD within 16 weeks of treatment and induced rapid reduction of itch. The safety profile remained consistent with prior findings from baricitinib clinical development in AD, with no new safety concerns.

ClinicalTrials.gov Identifiers: NCT03334396 (BREEZE-AD1), NCT03334422 (BREEZE-AD2)

INTRODUCTION

Atopic dermatitis (AD) is a chronic, heterogeneous inflammatory skin disease affecting up to 25% of children and 2-7% of adults globally.¹⁻³ AD is characterized by excessive T cell activation influenced by genetic and environmental factors, leading to significant skin infiltration by T cells and dendritic cells.⁴⁻⁷ Key cytokines in the pathogenesis of AD, such as thymic stromal lymphopoietin, interleukin (IL)-4, IL-13, IL-22, and IL-31, activate receptors which signal through intracellular Janus kinases JAK1/JAK2/tyrosine kinase 2.^{4,8-10} AD treatment with baricitinib, an oral selective JAK1 and JAK2 inhibitor, may modulate many cytokines involved in AD pathogenesis, thereby mitigating disease signs and symptoms.¹¹

Baricitinib is under investigation as a therapy for moderate-to-severe AD patients with an inadequate response to topical corticosteroids (TCS). In a 16-week Phase 2 trial of baricitinib in moderate-to-severe AD, significantly more patients treated with baricitinib 4-mg and TCS achieved Eczema Area and Severity Index (EASI)-50 and improvements in pruritus and reduced sleep loss compared with placebo.¹² The subsequent Phase 3 program explores baricitinib monotherapy, in combination with TCS, and as long-term therapy. Here we report the 16-week efficacy and safety data from the first two Phase 3 studies of baricitinib as monotherapy in moderate-to-severe AD.

PATIENTS and METHODS

Study Design and Oversight

BREEZE-AD1 (NCT03334396) and BREEZE-AD2 (NCT03334422) were independent 16-week randomised, double-blind, parallel-group, placebo-controlled trials conducted at 173 sites in Europe, Asia, Latin America, and Australia. Patients were randomised 2:1:1:1 to once-daily placebo, baricitinib 1-mg, 2-mg, or 4-mg (Fig. S1). Randomisation was stratified by geography and baseline disease severity. Treatment allocation was blinded to patients and investigators. At each visit, double-blind investigational products, including identical matching placebo tablets, were assigned by an interactive web response system. The Investigator's Global Assessment used was the Validated Investigator's Global Assessment of AD [vIGA-ADTM].¹³

Prior to randomisation, AD treatments were washed-out; 4 weeks for systemic and 2 weeks for topical treatments. Systemic and topical treatments were allowed as rescue therapy, initiated at any time, at the investigator's discretion, if patients experienced worsening or unacceptable AD symptoms. Emollient use was required throughout the trials; at least twice daily use was recommended prior to rescue. Patients completing the studies could enter a double-blinded long-term extension (LTE) study, BREEZE-AD3 (NCT03334435).

The trials were sponsored by Eli Lilly and Company (Lilly), under license from Incyte Corporation, and designed by Lilly personnel and an academic advisory board, including authors external to Lilly. The studies were conducted in accordance with ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines and approved by institutional review boards or ethics committees at each site (Table S1). Eligible patients provided written informed consent. BREEZE-AD1 was conducted from November 2017–January 2019; BREEZE-AD2 was conducted from November 2017–December 2018. Patients were enrolled from December 2017–August 2018 in both trials.

Patients

Patients were ≥18-years-old and had an AD diagnosis, defined by the American Academy of Dermatology criteria for ≥12 months before screening.¹⁴ Within 6 months before screening, patients had to have a documented history of an inadequate response to topical therapies (i.e., inability to achieve mild disease after use of at least a medium-potency TCS for ≥4 weeks, or for the maximum duration recommended by the product prescribing information [e.g., 14 days for super-potent TCS], whichever is shorter. Failure to

respond to systemic immunosuppressant therapies within 6 months of screening, or clinically significant adverse reactions to TCS, were considered surrogates for inadequate response to topical therapies. At screening and baseline, patients were required to have an EASI score ≥ 16 , vIGA-AD score ≥ 3 , and $\geq 10\%$ Body Surface Area involvement. Exclusion criteria included history of other concomitant skin conditions that could affect assessment of AD lesions, history of eczema herpeticum (EH) within 12 months before screening or ≥ 2 episodes of EH previously, a venous thromboembolic event (VTE) or major adverse cardiovascular event (MACE) within 12 weeks of screening or history of recurrent VTE, or clinically significant comorbidity at randomisation, and selected laboratory abnormalities. Additional criteria are available online as Supplemental Files.

Efficacy Outcomes

The primary endpoint tested the superiority of 4-mg or 2-mg once-daily over placebo in the treatment of moderate-to-severe AD patients (i.e., the proportion of patients achieving a vIGA-AD score of 0 [clear] or 1 [almost clear] with a ≥ 2 -point improvement from baseline at Week 16). The vIGA-AD, a static, 5-point scale from 0 (clear)–4 (severe), assesses the physician's impression of overall disease severity.¹³

Key secondary endpoints included: at 16 weeks, the proportion of 1-mg-treated patients achieving vIGA-AD (0, 1), proportion of baricitinib-treated patients achieving 75% and 90% improvement in EASI score (EASI75, EASI90), percent change from baseline in total EASI score, 75% improvement in the SCORing Atopic Dermatitis index (SCORAD75), mean change from baseline in the Skin Pain Numeric Rating Scale (NRS); at weeks 1, 2, 4, and 16, proportion of patients achieving a ≥ 4 -point improvement in the Itch NRS; at weeks 1 and 16, mean change from baseline in the Item 2 score of the Atopic Dermatitis Sleep Scale (ADSS). The Itch NRS and Skin Pain NRS were 11-point scales (0=no itch/pain and 10=worst itch/pain imaginable) where patients rated the worst severity in the previous 24 hours using a daily diary. Other patient-reported measures (Patient Oriented Eczema Measure [POEM] and the Dermatology Life Quality Index [DLQI]) were obtained at Weeks 1, 2, 4, 8, 12, and 16, with the exception of Week 12 for the DLQI.

Safety Assessments

Clinical laboratory tests, vital signs, and other safety assessments were performed at scheduled visits. The incidence and description of all adverse events (AEs) were recorded. An independent data-monitoring

committee composed of members external to Lilly regularly reviewed safety data. An independent, blinded, clinical-event committee adjudicated potential cardiovascular events, VTE, and deaths.

Statistical Analysis

Randomisation of approximately 600 patients in each independent study was estimated to provide >90% power to detect a difference in the comparison of vIGA-AD (0, 1) response rates at Week 16 between 4-mg and placebo and 2-mg and placebo, assuming a placebo response rate of 10% and a 20% risk difference between 4-mg and placebo. Primary and key secondary endpoint testing was adjusted for multiplicity, through a graphical testing scheme,¹⁵ to control for the overall family-wise Type I error rate at a 2-sided alpha level of 0.05 (Figure S2 and S3).

The intent-to-treat population included all randomised patients. A logistic regression model with region, baseline disease severity (vIGA-AD), baseline value of the variable of interest, and treatment group was used to compare categorical efficacy endpoints and health-outcomes variables. P-values from logistic regression models were reported. A mixed-model repeated measures analysis (MMRM) compared all continuous efficacy and health-outcomes variables with treatment, region, baseline disease severity (vIGA-AD), visit, and treatment as fixed, categorical effects and baseline-by-visit interaction as fixed continuous effects.

All efficacy and health-outcome data were analysed using two censoring rules. The primary censoring rule ('monotherapy') censored data after permanent study drug discontinuation or after rescue therapy with TCS (any potency) or systemic therapy. For categorical endpoints, a nonresponder imputation was applied at censoring; for continuous endpoints, data after rescue were censored as missing and MMRM analyses were then performed. The secondary censoring rule ('with TCS rescue') did not consider data as missing after TCS use. Data were only censored as missing after permanent study drug discontinuation or after initiating systemic rescue therapies.

Safety analyses were performed on all randomised patients who received ≥ 1 dose of study drug based on initial study drug assignment.

RESULTS

Patients

624 patients were enrolled in BREEZE-AD1 and 615 patients were enrolled in BREEZE-AD2 (Fig. S4 and S5). Baseline demographic and clinical characteristics were similar among treatment groups (Table 1). At

baseline, 40% and 50% of patients had a vIGA-AD score of 4 in BREEZE-AD1 and BREEZE-AD2; however, the baseline EASI and SCORAD scores were similar between studies. Study discontinuation rates were numerically lower in the 4-mg groups versus placebo (Fig S4). Of patients who completed BREEZE-AD1 and BREEZE-AD2, 86.9% and 88.0% entered the ongoing, LTE study, BREEZE-AD3 (Figs S4 and S5).

Primary Outcome

The primary analysis was conducted using monotherapy data, adjusted for multiplicity. In both trials, baricitinib 2-mg and 4-mg achieved a significant improvement versus placebo for the proportion of patients achieving vIGA-AD (0, 1) at Week 16 (Table 2, Fig. 1). The percentage of patients achieving vIGA-AD (0, 1) was 4.8% for placebo, 11.8% for 1-mg, 11.4% for 2-mg, and 16.8% (1-mg and 2-mg, $P \leq 0.05$; 4-mg, $P \leq 0.001$ vs. placebo) in BREEZE AD1, and 4.5% for placebo, 8.8% for 1-mg, 10.6% for 2-mg, and 13.8% for 4-mg (2-mg, $P \leq 0.05$; 4-mg, $P \leq 0.001$ vs. placebo) in BREEZE AD2.

Key Secondary Outcomes

Baricitinib 4-mg showed significant improvement for all key secondary endpoints. Within the graphical testing scheme, key clinician-reported outcomes tested at Week 16 included percent change from baseline in EASI score, proportion of patients achieving EASI75 (Fig. 2), proportion of patients achieving EASI90 (Fig. S6), and proportion of patients achieving SCORAD75 (Fig. S7); patient-reported outcomes (PROs) included proportion of patients with ≥ 4 -point improvement from baseline in Itch NRS at Weeks 1, 2, 4, and 16; change from baseline of ADSS item 2 (reduction in the number of nighttime awakenings due to itch) at Weeks 1 and 16; and change from baseline in Skin Pain NRS at Week 16 (Figs. 3 and 4).

In BREEZE-AD2, 2-mg showed significant improvement for all key secondary endpoints when adjusting for multiplicity, except in the proportion of patients achieving ≥ 4 -point improvement from baseline in Itch NRS at Week 1 (Table 2, Fig. S3).

In BREEZE-AD1, 2-mg was positive within the graphical testing scheme for the proportion of patients achieving EASI75 (Fig. S2); all other gated endpoints failed. Outside of the graphical testing scheme for multiplicity, 2-mg achieved a nominal level of significance ($P < 0.05$) compared to placebo for several additional key clinician-reported outcomes and PROs, including EASI percent change from baseline, EASI90, SCORAD75, ADSS item 2 at Week 1, and proportion of patients with ≥ 4 -point improvement in Itch NRS at Weeks 4 and 2. (Table 2, Fig 3).

Baricitinib 4-mg and 2-mg showed significant improvement for key secondary endpoints involving different AD domains; 1-mg treatment showed improvement in some secondary efficacy outcomes versus placebo, but did not achieve statistical significance consistently. Data with TCS rescue also showed inconsistent efficacy in the 1-mg dose. Summarizing across both trials, the numbers needed to treat (NNT) for 2-mg and 4-mg, respectively, were 16 and 10 for vIGA (0,1), 10 and 7 for EASI75, and 14 and 8 for the proportion of patients with an Itch 4-point improvement (Table S2). Results from additional secondary endpoints are reported in Table S3 and Figure S10.

Additional Efficacy Analyses

Baricitinib 4-mg and 2-mg were effective at improving health-related quality of life (HRQoL) from Week 1 and through Week 16 versus placebo. Significant improvements in the DLQI were seen at every time point assessed for the proportion of patients achieving DLQI total score of 0 to 1, indicating no effect on a patient's HRQoL ($P \leq 0.05$ vs placebo, all comparisons) (Fig. S8). For both 4-mg and 2-mg, the total change from baseline in the POEM score and the proportion of patients achieving ≥ 4 -point improvement from baseline were greater than placebo at Week 1 and throughout the studies ($P \leq 0.05$, all comparisons; Fig. 5). Baricitinib 4-mg and 2-mg also showed improvement in EASI50 in both trials (Fig. 4E-F). Change from baseline in total EASI score is reported in supplementary Figure S9.

Rescue Therapy

In both trials, more placebo-treated patients were rescued versus baricitinib-treated patients, with a higher overall rescue rate observed in BREEZE-AD2 versus BREEZE-AD1 (Table S4). Most patients required TCS as rescue therapy; rescue to systemic therapies occurred in 2.2%, 2.4%, 2.0%, and 0.4% of rescued patients in the placebo, 1-mg, 2-mg, and 4-mg groups. Placebo-treated patients required rescue much earlier than baricitinib-treated patients. This difference resulted in reduction in the amount of total sponsor-provided low-moderate TCS in BREEZE-AD1 and BREEZE-AD2 (Table S5).

The endpoints with both the monotherapy and TCS rescue censoring rules are presented in Table 2 to show the overall pattern of response. With the monotherapy rule, patients who met a categorical endpoint but were rescued to TCS were censored; because of the nonresponder imputation, the proportion of patients meeting the endpoint decreases over time. These data were not removed in the TCS rescue rule. With the TCS rescue rule, 4-mg also showed significant improvement versus placebo for key secondary endpoints ($P < 0.05$). With TCS rescue censoring rules in BREEZE-AD1, 2-mg was superior versus placebo for Itch ≥ 4 -point improvement from baseline and ADSS Item 2 at Week 16 (Table 2, Fig. 3).

Safety

Treatment-emergent AEs were reported in 54%, 54%, 58%, and 58% of patients and in 56%, 53%, 58%, and 54% of patients on placebo, 1-mg, 2-mg, and 4-mg in BREEZE-AD1 and BREEZE-AD2.

Nasopharyngitis, upper-respiratory tract infections (URIs), creatine phosphokinase (CPK) elevations, and headaches were the most frequently reported AEs ($>2\%$ in any treatment group; Table 3). There was no increase in frequency of nasopharyngitis and URIs with baricitinib versus placebo. Headaches were reported in 8.0% and 8.9% of 4-mg-treated patients versus 6.4% and 2.0% of placebo-treated patients in BREEZE-AD1 and BREEZE-AD2. Headaches were mild (76% of reported cases) and short-lived (median: 0.5 days), with none requiring study drug interruption or discontinuation. Herpes simplex was observed more often with baricitinib in BREEZE-AD1. Most cases were of mild-or-moderate severity in both studies and did not cause serious AEs (SAEs) or drug discontinuation (Table 3). Across the studies, there was 1 case (0.2%) of herpes zoster in the combined placebo group and 2 cases (0.8%) in the combined baricitinib 2 mg group. As seen in previous baricitinib studies, CPK elevations were asymptomatic and either resolved to below the upper limit of normal, or were resolving during the study without treatment interruption (16 of 20 cases with Common Terminology Criteria for Adverse Events [CTCAE] grade 3 or higher on baricitinib).¹² Three baricitinib patients had temporary treatment interruption with resolution of CPK elevations; 1 patient discontinued the study. In

placebo, of 10 patients with CPK elevations (CTCAE grade 3 or higher), 8 patients resolved or were resolving during the study without treatment interruption; 2 patients required temporary treatment interruption.

Grade 3 or 4 CPK elevations were seen in 1.6%, 2.4%, 3.3%, and 2.4% of patients and in 2.1%, 1.7%, 1.7%, and 4.9% of patients on placebo, 1-mg, 2-mg, and 4-mg in BREEZE-AD1 and BREEZE-AD2.

During the 16-week placebo-controlled period, 6 (1.2%) placebo-treated, 9 (3.6%) 1-mg-treated, 4 (1.6%) 2-mg-treated, and 3 (1.2%) 4-mg-treated patients discontinued the studies due to AEs. During the treatment period, 15 (3.0%) SAEs were reported with placebo versus 10 (4%), 3 (1.2%), and 3 (1.2%) in the 1-mg, 2-mg, and 4-mg groups. Two malignancies (1 breast cancer and 1 papillary thyroid cancer) were reported on placebo; both patients discontinued from the study. There were no clusters of SAEs and no overall differences in frequency of SAEs by treatment (Table S6). No deaths, gastrointestinal perforations, MACE, VTE (deep vein thrombosis or pulmonary embolism) or opportunistic infections were reported in either trial. No clinically meaningful changes in haemoglobin, neutrophil, lymphocyte, and platelet counts were observed in the study groups. Figure S11 shows CTCAE grade increases for selected laboratory analytes through 16 weeks.

DISCUSSION

BREEZE-AD1 and BREEZE-AD2 are part of a larger clinical development program investigating the efficacy of baricitinib for adults with moderate-to-severe AD. As the first trials of this program, baricitinib administered as monotherapy offered significant benefit over placebo on clinically important measures of disease severity, including skin inflammation (vIGA-AD [0,1], EASI75, SCORAD75), itch, sleep disturbance, and skin pain at multiple time points during the studies. For 4-mg, significant improvements were evident at Week 1 for skin inflammation (EASI75), itch, sleep disturbance, and skin pain. The treatment benefits were larger with 4-mg in both trials than with 2-mg; 1-mg showed inconsistent efficacy.

Availability of more-effective and safer options for long-term AD treatments remains an unmet need.^{5,16} Until recently, treatments for moderate-to-severe AD were mainly TCS and topical calcineurin inhibitors,¹⁷ with broad systemic immunosuppressants like cyclosporine, azathioprine, or methotrexate.¹⁸ Dupilumab, a subcutaneously administered anti-IL-4 receptor α -antagonist monoclonal antibody, was approved for AD treatment in 2017.^{19,20} Baricitinib, a selective JAK1 and 2 inhibitor, is the first-in-its-class oral therapy showing significant improvement in AD signs and symptoms in Phase 3 trials in adults with moderate-to-severe disease, widening therapeutic choices for this population. In addition to the current trials, a third trial of baricitinib in combination with TCS has recently completed (NCT03559270).²¹ Thus, the inhibition of JAK1/JAK2 appears to be an appropriate target in AD treatment. Additional placebo-controlled AD studies are ongoing for baricitinib as monotherapy (NCT03435081) and TCS combination therapy (NCT03428100).

Pruritus, a major AD symptom,²² showed significant and rapid improvement with 4-mg as early as Week 1 and continued to show improvement through Week 16 versus placebo. Numerically higher improvements in pruritus were observed with 2-mg through Week 16. Two additional novel PROs were utilized to capture symptoms beyond itch: skin pain and the impact of itch on sleep.²³ These studies support evidence that AD symptom burden extends beyond itch, with patients showing high baseline levels of patient-reported skin pain (Skin Pain NRS at baseline range of 5.5–6.2 of 10) and difficulty in falling and staying asleep due to itch (average nightly awakenings of 1.6–3.4 events/night due to itch). In both studies, baricitinib improved pain and sleep at 1 week after starting therapy, with associated improvements in HRQoL assessment (DLQI) and patient-reported severity (POEM).

Overall, AEs and SAEs were similar between placebo and baricitinib groups. The common on-treatment AEs reported with baricitinib were nasopharyngitis, headache, increased blood CPK levels, and URI. Headache and CPK elevation showed a numeric increase in frequency in baricitinib groups versus placebo.

Most headache events were short in duration and resolved in all groups, while CPK elevations were asymptomatic. CPK elevations are observed in most trials of JAK inhibitors.^{24,25} Although the mechanisms are unknown, there were no reported clinical effects associated with the CPK elevations in BREEZE-AD1 and BREEZE-AD2. Herpes simplex cases were reported more often with baricitinib in BREEZE-AD1 but not in BREEZE-AD2 (none resulted in study drug discontinuation). Further study will better quantify any potential increase in Herpes simplex with baricitinib. During the 16-week treatment period in these trials, no deaths, MACE, or VTE occurred with baricitinib, and two malignancies occurred with placebo. Based on mechanism of action, JAK2 inhibition could lead to reduction in haemoglobin and neutrophils.^{8,11} However, no grade 3 or 4 anemia, neutropenia, or lymphopenia occurred during the initial 16 weeks of 2-mg or 4-mg treatment, suggesting the degree of JAK2 inhibition by the 4-mg dose did not result in clinically impactful changes in haematology parameters. Additional results from ongoing Phase 3 trials and long-term safety follow-up are required for a comprehensive safety assessment.

Limitations include the predominance of Caucasian patients in the large, global population. Patients in BREEZE-AD2 had higher baseline disease severity, with a larger proportion having severe disease by vIGA-AD (~50%) compared to BREEZE-AD1 (40%). This may account for the higher rescue rate and lower response observed in BREEZE-AD2. Additionally, although a washout period from AD therapies is usually required for safety and to avoid rebound from previous treatments at randomisation, the combination of washout with TCS rescue during the studies at the investigator's discretion may have contributed to a high rescue rate earlier during treatment, before some patients experienced benefit from baricitinib. In addition, a decrease over time in the response rate for categorical endpoints (e.g., EASI50 and POEM ≥ 4 -point improvement from baseline) was observed with the monotherapy data in part because patients who had achieved these endpoints before rescue were considered missing when rescued later in the study. Higher and more sustained responses were noted when data after rescue therapy are used in the analysis as shown by the TCS rescue figures.

In summary, in two independent Phase 3 studies, once-daily, oral baricitinib monotherapy was superior to placebo for clinical signs, patient-reported symptoms, and HRQoL in moderate-to-severe AD. No unexpected safety concerns were reported with baricitinib. Baricitinib may represent a first-in-class oral treatment option for adult, moderate-to-severe AD patients.

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Figure legends

Figure 1. Proportion of patients achieving validated Investigator's Global Assessment of atopic dermatitis (vIGA-AD) of 0 or 1 in BREEZE-AD1 (a, c) and BREEZE-AD2 (b, d) trials.

TCS, topical corticosteroids.

^aData were censored after rescue or after permanent study drug discontinuation and imputed using nonresponder imputation.

^bIncludes observed values up to permanent study drug discontinuation.

* $P \leq 0.05$, ** $P \leq 0.01$ and *** $P \leq 0.001$ for analyses comparing baricitinib with placebo.

Figure 2. Percent change from baseline in total Eczema Area and Severity Index (EASI) score in BREEZE-AD1 (a) and BREEZE-AD2 (b). Proportion of patients achieving 75% improvement in EASI (EASI75) in BREEZE-AD1 (c, e) and BREEZE-AD2 (d, f).

TCS, topical corticosteroids.

^aData collected after rescue therapy or after permanent study drug discontinuation are censored and set to missing. For continuous endpoints, LS means are from MMRM analyses, which incorporates multiple imputation for missing data. For categorical endpoints, a nonresponder imputation was applied at censoring.

^bIncludes observed values up to permanent study drug discontinuation.

* $P \leq 0.05$, ** $P \leq 0.01$ and *** $P \leq 0.001$ for analyses comparing baricitinib with placebo.

Figure 3. Percent change from baseline in Itch NRS in BREEZE-AD1 (a) and BREEZE-AD2 (b). Proportion of patients achieving a ≥ 4 -point improvement in Itch NRS^c in BREEZE-AD1 (c, e) and BREEZE-AD2 (d, f).

N, number of patients in the analysis population; NRS, Numeric Rating Scale; TCS, topical corticosteroids.

^aData collected after rescue therapy or after permanent study drug discontinuation are censored and set to missing. For continuous endpoints, LS means are from MMRM analyses, which incorporates multiple imputation for missing data. For categorical endpoints, a nonresponder imputation was applied at censoring.

^bIncludes observed values up to permanent study drug discontinuation.

^cFor these analyses, placebo N=222, 1-mg N=105, 2-mg N=100 and 4-mg N=107 in BREEZE-AD1, and placebo N=213, 1-mg N=100, 2-mg N=106 and 4-mg N=107 in BREEZE-AD2, since not all patients had at least a 4-point score at baseline.

* P≤0.05, ** P≤0.01 and *** P≤0.001 for analyses comparing baricitinib with placebo.

Figure 4. Mean change from baseline in ADSS Item 2 in BREEZE-AD1 (a) and BREEZE-AD2 (b), mean change from baseline in Skin Pain NRS in BREEZE-AD1 (c) and BREEZE-AD2 (d), and proportion of patients with EASI50 response in BREEZE-AD1 (e) and BREEZE-AD2 (f).

ADSS, Atopic Dermatitis Sleep Scale; EASI, Eczema Area and Severity Index; NRS, Numeric Rating Scale.

Data reported from monotherapy analysis. Data collected after rescue therapy or after permanent study drug discontinuation are censored and set to missing. For continuous endpoints, LS means are from MMRM analyses, which incorporates multiple imputation for missing data. For categorical endpoints, a nonresponder imputation was applied at censoring. .

* P≤0.05, ** P≤0.01 and *** P≤0.001 for analyses comparing baricitinib with placebo

Figure 5. Mean change from baseline in total POEM score in BREEZE-AD1 (a) and BREEZE-AD2 (b); and proportion of patients achieving ≥4-point improvement in POEM^c in BREEZE-AD1 (c) and BREEZE-AD2 (d).

N, number of patients in the analysis population; POEM, Patient Oriented Eczema Measures.

Data reported from monotherapy analysis. Data collected after rescue therapy or after permanent study drug discontinuation are censored and set to missing. For continuous endpoints, LS means are from MMRM analyses, which incorporates multiple imputation for missing data. For categorical endpoints, a nonresponder imputation was applied at censoring.

^cFor these analyses, placebo N=247, 1-mg N=127, 2-mg N=123 and 4-mg N=125 in BREEZE-AD1, and placebo N=240, 1-mg N=124, 2-mg N=122 and 4-mg N=121 in BREEZE-AD2, since not all patients had at least a 4-point score at baseline.

* P≤0.05, ** P≤0.01 and *** P≤0.001 for analyses comparing baricitinib with placebo.

Table 1. Baseline patient demographics and disease characteristics

	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 (year)	35 (12.6)	36 (12.4)	35 (13.7)	37 (12.9)	35 (13.0)	33 (10.0)	36 (13.2)	34 (14.1)
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)
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)
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)
Duration since AD diagnosis (year)	26 (15.5)	27 (14.9)	25 (14.6)	25 (14.9)	25 (13.9)	24 (12.7)	24 (13.8)	23 (14.8)
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)
BMI (kg/m ²)	25 (4.5)	25 (4.6)	25 (5.1)	25 (4.3)	25 (4.3)	26 (5.2)	25 (5.0)	25 (4.2)
Geographic Region, n (%)								
Europe	135 (54.2)	67 (52.8)	67 (54.5)	68 (54.4)	111 (45.5)	57 (45.6)	56 (45.5)	56 (45.5)
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)
Other ^a	69 (27.7)	37 (29.1)	35 (28.5)	35 (28.0)	88 (36.1)	46 (36.8)	45 (36.6)	44 (35.8)
vIGA-AD ^b 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)
EASI ^c	32 (13.0)	29 (11.8)	31 (11.7)	32 (12.7)	33 (12.8)	33 (12.7)	35 (16.0)	33 (12.7)
SCORAD ^d	68 (14.0)	66 (14.4)	68 (13.0)	68 (12.9)	68 (12.7)	67 (12.9)	69 (13.3)	68 (13.6)
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)
Itch NRS ^e	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)
Skin Pain NRS ^f	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)
ADSS item 2 ^g	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)
POEM ^h	21 (5.6)	20 (5.6)	21 (5.6)	21 (5.6)	21 (6.3)	20 (6.5)	21 (6.0)	20 (6.3)
DLQI ⁱ	14 (7.4)	13 (6.8)	13 (7.7)	14 (7.1)	15 (8.1)	15 (8.1)	14 (7.7)	14 (8.4)

ADSS, Atopic Dermatitis Sleep Scale; Bari, baricitinib; BMI, body mass index; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; NRS, Numeric Rating Scale; PBO, placebo; POEM, Patient Oriented Eczema Measures; SCORAD, SCORing Atopic Dermatitis; SD, standard deviation; vIGA-AD, Validated Investigator's Global Assessment of atopic dermatitis.

Data reported as mean (SD) unless otherwise noted.

^aOther: For BREEZE-AD1: India, Mexico, and Taiwan and for BREEZE-AD2: Argentina, Australia, Israel, South Korea

^bIGA-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).

^cEASI scores range from 0 to 72, with higher scores indicating greater severity.

^dSCORAD 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 to 103.

^eItch NRS, ranging from 0 (no itch) to 10 (worst itch imaginable).

^fSkin Pain NRS, ranging from 0 (no pain) to 10 (worst pain).

^gADSS item 2 assesses the frequency of night-time awakenings due to itch the previous night on a scale of 0 to 29.

^hPOEM 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 to 28.

ⁱDLQI evaluates health-related quality of life on a scale of 0 to 30.

Table 2. Summary of primary and key secondary endpoints at Week 16 (Table 2a: BREEZE-AD1 and Table 2b: BREEZE-AD2)

Table 2a.	Monotherapy ^a				With TCS rescue ^b			
	PBO	Bari 1-mg	Bari 2-mg	Bari 4-mg	PBO	Bari 1-mg	Bari 2-mg	Bari 4-mg
BREEZE-AD1	(N=249)	(N=127)	(N=123)	(N=125)	(N=244)	(N=125)	(N=123)	(N=123)
viGA-AD of 0 or 1, % (n)	4.8% (12)	11.8% (15)	11.4% (14)	16.8% (21)	10.0% (25)	16.5% (21)	17.1% (21)	22.4% (28)
95% CI	2.8%, 8.2%	7.3%, 18.6%	6.9%, 18.2%	11.3%, 24.3%	6.9%, 14.4%	11.1%, 24.0%	11.4%, 24.7%	16.0%, 30.5%
p-value vs. placebo		0.014	0.020	<0.001		0.065	0.049	0.002
OR (95% CI) vs. placebo		2.7 (1.2, 6.0)	2.6 (1.2, 5.8)	4.1 (1.9, 8.7)		1.8 (1.0, 3.4)	1.9 (1.0, 3.6)	2.7 (1.5, 4.9)
EASI75, % (n)	8.8% (22)	17.3% (22)	18.7% (23)	24.8% (31)	19.7% (49)	28.3% (36)	32.5% (40)	36.0% (45)
95% CI	5.9%, 13.0%	11.7%, 24.8%	12.8%, 26.5%	18.1%, 33.0%	15.2%, 25.1%	21.2%, 36.7%	24.9%, 41.2%	28.1%, 44.7%
p-value vs. placebo		0.032	0.006	<0.001		0.104	0.007	<0.001
OR (95% CI) vs. placebo		2.0 (1.1, 3.9)	2.5 (1.3, 4.7)	3.7 (2.0, 6.9)		1.5 (0.9, 2.5)	2.0 (1.2, 3.3)	2.4 (1.5, 3.9)
EASI90, % (n)	4.8% (12)	8.7% (11)	10.6% (13)	16.0% (20)	6.8% (17)	11.8% (15)	13.8% (17)	20.0% (25)
95% CI	2.8%, 8.2%	4.9%, 14.8%	6.3%, 17.2%	10.6%, 23.4%	4.3%, 10.7%	7.3%, 18.6%	8.8%, 21.0%	13.9%, 27.9%
p-value vs. placebo		0.210	0.029	<0.001		0.151	0.025	<0.001
OR (95% CI) vs. placebo		1.7 (0.7, 4.1)	2.5 (1.1, 5.7)	4.1 (1.9, 8.9)		1.7 (0.8, 3.6)	2.3 (1.1, 4.7)	3.7 (1.9, 7.3)
Percent change from baseline in total EASI score, LSM (SE)	-34.8 (3.6)	-48.2 (4.5)	-51.9 (4.3)	-59.4 (3.8)	-39.2 (2.3)	-52.2 (3.2)	-55.2 (3.2)	-60.7 (3.1)
LSM difference from placebo (SE)		-13.4 (5.8)	-17.1 (5.6)	-24.5 (5.2)		-13.1 (3.9)	-16.0 (3.9)	-21.6 (3.8)
LSM Difference from placebo, 95% CI		-24.8, -2.0	-28.1, -6.1	-34.8, -14.2		-20.7, -5.5	-23.7, -8.4	-29.1, -14.0
p-value vs. placebo		0.021	0.002	<0.001		<0.001	<0.001	<0.001
SCORAD75, % (n)	1.2% (3)	5.5% (7)	7.3% (9)	10.4% (13)	2.4% (6)	7.1% (9)	11.4% (14)	12.8% (16)
95% CI	0.4%, 3.5%	2.7%, 10.9%	3.9%, 13.3%	6.2%, 17.0%	1.1%, 5.2%	3.8%, 12.9%	6.9%, 18.2%	8.0%, 19.8%

p-value vs. placebo		0.025	0.004	<0.001	0.034		<0.001	<0.001
OR (95% CI) vs. placebo		4.3 (1.2, 15.2)	6.1 (1.8, 21.0)	8.8 (2.7, 28.6)	3.0 (1.1, 8.3)		5.1 (2.0, 13.0)	5.7 (2.2, 14.4)
≥4-point improvement in Itch NRS at	7.2% (16)	10.5% (11)	12.0% (12)	21.5% (23)	20.3% (45)	25.7% (27)	31.0% (31)	29.9% (32)
Week 16, % (n)								
95% CI	4.5%, 11.4%	6.0%, 17.8%	7.0%, 19.8%	14.8%, 30.2%	15.5%,	18.3%, 34.8%	22.8%, 40.6%	22.1%, 39.2%
p-value vs. placebo		0.246	0.169	<0.001	26.0%	0.099	0.032	0.027
OR (95% CI) vs. placebo		1.6 (0.7, 3.6)	1.7 (0.8, 3.8)	3.6 (1.8, 7.2)	1.6 (0.9, 2.8)		1.8 (1.1, 3.2)	1.9 (1.1, 3.2)
≥4-point improvement in Itch NRS at	2.7% (6)	9.5% (10)	12.0% (12)	22.4% (24)	8.6% (19)	13.3% (14)	15.0% (15)	26.2% (28)
Week 4, % (n)								
95% CI	1.2%, 5.8%	5.3%, 16.6%	7.0%, 19.8%	15.6%, 31.2%	5.5%, 13.0%	8.1%, 21.1%	9.3%, 23.3%	18.8%, 35.2%
p-value vs. placebo		0.009	0.002	0.001	0.103		0.092	<0.001
OR (95% CI) vs. placebo		3.8 (1.4, 10.5)	4.6 (1.7, 12.2)	10.0 (4.1, 24.6)	1.8 (0.9, 3.8)		1.9 (0.9, 3.8)	3.9 (2.1, 7.5)
≥4-point improvement in Itch NRS at	0	5.7% (6)	8.0% (8)	15.9% (17)	0.5% (1)	6.7% (7)	8.0% (8)	15.9% (17)
Week 2, % (n)								
95% CI	0.0%, 0.0%	2.6%, 11.9%	4.1%, 15.0%	10.2%, 24.0%	0.1%, 2.5%	3.3%, 13.1%	4.1%, 15.0%	10.2%, 24.0%
p-value vs. placebo		0.019	0.009	<0.001	0.006		0.003	<0.001
OR (95% CI) vs. placebo		29.0 (1.8, >100)	40.1 (2.5, >100)	88.3 (5.7, >100)	11.5 (2.0, 65.0)		13.3 (2.4, 73.8)	29.6 (5.7, >100)
≥4-point improvement in Itch NRS at	0	1.9% (2)	0	6.5% (7)	0	1.9% (2)	0	6.5% (7)
Week 1, % (n)								
95% CI	0.0%, 0.0%	0.5%, 6.7%	0.0%, 0.0%	3.2%, 12.9%	0.0%, 0.0%	0.5%, 6.7%	0.0%, 0.0%	3.2%, 12.9%
p-value vs. placebo		0.097	0.681	0.010	0.097		0.681	0.010
OR (95% CI) vs. placebo		10.7 (0.7, >100)	2.1 (0.1, 78.1)	31.9 (2.3, >100)	10.7 (0.7, >100)		2.1 (0.1, 78.1)	31.9 (2.3, >100)
Change from baseline in Item 2 of the	-0.84 (0.2)	-1.21 (0.2)	-1.04 (0.2)	-1.42 (0.2)	-0.87 (0.2)	-1.65 (0.2)	-1.54 (0.2)	-1.79 (0.2)

ADSS at Week 16, LSM (SE)								
LSM difference from placebo (SE)		-0.4 (0.2)	-0.2 (0.2)	-0.6 (0.2)		-0.8 (0.3)	-0.7 (0.3)	-0.9 (0.3)
LSM Difference from placebo, 95% CI		-0.8, 0.1	-0.7, 0.2	-1.0, -0.2		-1.3, -0.2	-1.2, -0.1	-1.5, -0.4
p-value vs. placebo		0.103	0.352	0.006		0.004	0.015	<0.001
Change from baseline in Item 2 of the	0.11 (0.1)	-0.32 (0.2)	-0.30 (0.2)	-0.91 (0.2)	0.03 (0.1)	-0.39 (0.2)	-0.37 (0.2)	-0.98 (0.2)
ADSS at Week 1								
LSM difference from placebo (SE)		-0.4 (0.2)	-0.4 (0.2)	-1.0 (0.2)		-0.4 (0.2)	-0.4 (0.2)	-1.0 (0.2)
LSM Difference from placebo		-0.8, -0.1	-0.8, 0.0	-1.4, -0.7		-0.8, -0.1	-0.8, 0.0	-1.4, -0.6
(95% CI)		0.019	0.031	<0.001		0.022	0.031	<0.001
p-value vs. placebo								
Change from baseline in Skin Pain NRS,	-0.84 (0.2)	-1.92 (0.3)	-1.58 (0.3)	-1.93 (0.3)	-1.73 (0.2)	-2.27 (0.2)	-2.29 (0.2)	-2.57 (0.2)
LSM (SE)								
LSM difference from placebo (SE)		-1.1 (0.4)	-0.74 (0.4)	-1.1 (0.4)		-0.5 (0.3)	-0.6 (0.3)	-0.8 (0.3)
LSM Difference from placebo, 95% CI		-1.8, -0.3	-1.5, 0.0	-1.8, -0.4		-1.0, 0.0	-1.1, -0.1	-1.3, -0.3
p-value vs. placebo		0.005	0.051	0.002		0.039	0.032	0.001

Table 2b.	Monotherapy ^a				With TCS rescue ^b			
	PBO	Bari 1-mg	Bari 2-mg	Bari 4-mg	PBO	Bari 1-mg	Bari 2-mg	Bari 4-mg
BREEZE-AD2	(N=244)	(N=125)	(N=123)	(N=123)	(N=244)	(N=125)	(N=123)	(N=123)
vIGA-AD of 0 or 1, % (n)	4.5% (11)	8.8% (11)	10.6% (13)	13.8% (17)	11.1% (27)	12.0% (15)	19.5% (24)	22.0% (27)
95% CI	2.5%, 7.9%	5.0%, 15.1%	6.3%, 17.2%	8.8%, 21.0%	7.7%, 15.6%	7.4%, 18.9%	13.5%, 27.4%	15.5%, 30.1%
p-value vs. placebo		0.108	0.042	0.003		0.710	0.022	0.003
OR (95% CI) vs. placebo		2.1 (0.9, 5.0)	2.6 (1.1, 5.9)	3.6 (1.6, 8.1)		1.1 (0.6, 2.3)	2.1 (1.1, 3.8)	2.5 (1.4, 4.6)
EASI75, % (n)	6.1% (15)	12.8% (16)	17.9% (22)	21.1% (26)	18.9% (46)	28.0% (35)	36.6% (45)	35.8% (44)
95% CI	3.8%, 9.9%	8.0%, 19.8%	12.1%, 25.6%	14.9%, 29.2%	14.4%, 24.2%	20.9%, 36.4%	28.6%, 45.4%	27.9%, 44.6%
p-value vs. placebo		0.046	<0.001	<0.001		0.036	<0.001	<0.001
OR (95% CI) vs. placebo		2.4 (1.1, 4.9)	3.5 (1.7, 7.0)	4.4 (2.2, 8.8)		1.7 (1.0, 2.9)	2.6 (1.6, 4.3)	2.5 (1.5, 4.1)
EASI90, % (n)	2.5% (6)	6.4% (8)	8.9% (11)	13.0% (16)	6.6% (16)	9.6% (12)	17.9% (22)	22.0% (27)
95% CI	1.1%, 5.3%	3.3%, 12.1%	5.1%, 15.3%	8.2%, 20.1%	4.1%, 10.4%	5.6%, 16.0%	12.1%, 25.6%	15.5%, 30.1%
p-value vs. placebo		0.053	0.007	<0.001		0.256	<0.001	<0.001
OR (95% CI) vs. placebo		2.8 (1.0, 8.0)	3.9 (1.4, 10.4)	6.2 (2.4, 15.9)		1.6 (0.7, 3.4)	3.2 (1.6, 6.4)	4.2 (2.2, 8.2)
Percent change from baseline in total EASI score, LSM (SE)	-28.9 (4.3)	-41.7 (5.3)	-54.8 (5.0)	-54.9 (4.6)	-44.2 (2.5)	-51.0 (3.5)	-55.5 (3.5)	-57.6 (3.4)
LSM difference from placebo (SE)		-12.8 (6.8)	-25.9 (6.5)	-26.0 (6.2)		-6.8 (4.3)	-11.3 (4.3)	-13.4 (4.2)
LSM Difference from placebo, 95% CI		-26.2, 0.7	-38.8, -13.0	-38.3, -13.7		-15.2, 1.6	-19.7, -3.0	-21.7, -5.2
p-value vs. placebo		0.062	<0.001	<0.001		0.112	0.008	0.001
SCORAD75, % (n)	1.6% (4)	4.8% (6)	7.3% (9)	11.4% (14)	5.3% (13)	5.6% (7)	13.0% (16)	16.3% (20)
95% CI	0.6%, 4.1%	2.2%, 10.1%	3.9%, 13.3%	6.9%, 18.2%	3.1%, 8.9%	2.7%, 11.1%	8.2%, 20.1%	10.8%, 23.8%

p-value vs. placebo		0.086	0.006	<0.001	0.858		0.011	<0.001
OR (95% CI) vs. placebo		2.9 (0.9, 9.8)	5.0 (1.6, 15.5)	7.4 (2.5, 21.8)	1.1 (0.4, 2.7)		2.7 (1.3, 5.6)	3.4 (1.7, 7.0)
≥4-point improvement in Itch NRS at	4.7% (10)	6.0% (6)	15.1% (16)	18.7% (20)	23.0% (49)	18.0% (18)	34.9% (37)	33.6% (36)
Week 16, % (n)								
95% CI	2.6%, 8.4%	2.8%, 12.5%	9.5%, 23.1%	12.4%, 27.1%	17.9%,	11.7%, 26.7%	26.5%, 44.4%	25.4%, 43.0%
p-value vs. placebo		0.505	0.002	<0.001	29.1%	0.477	0.014	0.022
OR (95% CI) vs. placebo		1.4 (0.5, 3.9)	3.6 (1.6, 8.3)	4.9 (2.2, 10.9)	0.8 (0.4, 1.5)		2.0 (1.2, 3.3)	1.9 (1.1, 3.2)
≥4-point improvement in Itch NRS at	2.3% (5)	8.0% (8)	11.3% (12)	18.7% (20)	11.3% (24)	14.0% (14)	18.9% (20)	26.2% (28)
Week 4, % (n)								
95% CI	1.0%, 5.4%	4.1%, 15.0%	6.6%, 18.8%	12.4%, 27.1%	7.7%, 16.2%	8.5%, 22.1%	12.6%, 27.4%	18.8%, 35.2%
p-value vs. placebo		0.016	0.001	<0.001	0.317		0.036	<0.001
OR (95% CI) vs. placebo		3.9 (1.3, 11.6)	5.5 (2.0, 15.5)	9.9 (3.7, 26.4)	1.5 (0.7, 3.0)		2.1 (1.1, 4.0)	3.2 (1.7, 6.1)
≥4-point improvement in Itch NRS at	0.9% (2)	3.0% (3)	6.6% (7)	10.3% (11)	1.9% (4)	4.0% (4)	8.5% (9)	13.1% (14)
Week 2, % (n)								
95% CI	0.3%, 3.4%	1.0%, 8.5%	3.2%, 13.0%	5.8%, 17.5%	0.7%, 4.7%	1.6%, 9.8%	4.5%, 15.4%	8.0%, 20.8%
p-value vs. placebo		0.141	0.007	<0.001	0.204		0.005	<0.001
OR (95% CI) vs. placebo		3.3 (0.7, 16.5)	7.1 (1.7, 29.5)	11.0 (2.8, 42.9)	2.4 (0.6, 8.8)		5.1 (1.6, 15.9)	8.2 (2.8, 24.2)
≥4-point improvement in Itch NRS at	0.5% (1)	0	2.8% (3)	3.7% (4)	0.5% (1)	0% (0)	2.8% (3)	3.7% (4)
Week 1, % (n)								
95% CI	0.1%, 2.6%	0.0%, 0.0%	1.0%, 8.0%	1.5%, 9.2%	0.1%, 2.6%	0.0%, 0.0%	1.0%, 8.0%	1.5%. 9.2%
p-value vs. placebo		0.839	0.089	0.033	0.839		0.089	0.033
OR (95% CI) vs. placebo		0.7 (0.04, 14.3)	4.8 (0.8, 28.9)	6.7 (1.2, 38.0)	0.74 (0.0, 14.3)		4.8 (0.8, 28.9)	6.7 (1.2, 38.0)

Change from baseline in Item 2 of the ADSS at Week 16, LSM (SE)	-0.50 (0.1)	-0.78 (0.1)	-1.03 (0.1)	-1.13 (0.1)	-0.83 (0.1)	-1.10 (0.1)	-1.21 (0.1)	-1.38 (0.1)
LSM difference from placebo (SE)		-0.3 (0.2)	-0.5 (0.2)	-0.6 (0.2)		-0.3 (0.2)	-0.4 (0.2)	-0.6 (0.2)
LSM Difference from placebo, 95% CI		-0.6, 0.1	-0.9, -0.2	-1.0, -0.3		-0.6, 0.0	-0.7, -0.1	-0.8, -0.3
p-value vs. placebo		0.123	0.003	<0.001		0.074	0.011	<0.001
Change from baseline in Item 2 of the ADSS at Week 1, LSM (SE)	-0.02 (0.1)	-0.37 (0.1)	-0.37 (0.1)	-0.58 (0.1)	-0.09 (0.1)	-0.42 (0.1)	-0.44 (0.1)	-0.65 (0.1)
LSM difference from placebo (SE)		-0.4 (0.1)	-0.4 (0.1)	-0.6 (0.1)		-0.3 (0.1)	-0.4 (0.1)	-0.6 (0.1)
LSM Difference from placebo (95% CI)		-0.6, -0.1	-0.6, -0.1	-0.8, -0.3		-0.6, -0.1	-0.6, -0.1	-0.8, -0.3
p-value vs. placebo		0.003	0.003	<0.001		0.005	0.003	<0.001
Change from baseline in Skin Pain NRS, LSM (SE)	-0.86 (0.3)	-1.09 (0.3)	-2.61 (0.3)	-2.49 (0.3)	-1.96 (0.2)	-1.95 (0.2)	-2.85 (0.2)	-2.68 (0.2)
LSM difference from placebo (SE)		-0.2 (0.4)	-1.8 (0.4)	-1.6 (0.4)		0.0 (0.3)	-0.9 (0.3)	-0.7 (0.3)
LSM Difference from placebo, 95% CI		-1.1, 0.6	-2.5, -1.0	-2.4, -0.9		-0.5, 0.5	-1.4, -0.4	-1.2, -0.2
p-value vs. placebo		0.580	<0.001	<0.001		0.975	<0.001	0.006

ADSS, Atopic Dermatitis Sleep Scale; Bari, baricitinib; CI: confidence interval; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; LSM, least squares mean, N, number of subjects in the analysis population; n, number of subjects in the specified category; NRS, Numeric Rating Scale; PBO, placebo; POEM, Patient Oriented Eczema Measures; SCORAD, SCORing Atopic Dermatitis; SE: standard error; vIGA-AD, Validated Investigator's Global Assessment of atopic dermatitis.

Data reported as least squares mean change from baseline $\pm$ SE unless otherwise indicated. Endpoints assessed at Week 16, unless otherwise specified.

^aData collected after rescue therapy or after permanent study drug discontinuation are censored and set to missing. For continuous endpoints, LS means are from MMRM analyses, which incorporates multiple imputation for missing data. For categorical endpoints, a nonresponder imputation was applied at censoring

^bIncludes observed values up to permanent study drug discontinuation.

Table 3. Safety Data

	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=124)	Bari 2-mg (N=123)	Bari 4-mg (N=123)
Summary of Safety								
TEAE, any	135 (54.2)	69 (54.3)	71 (57.7)	73 (58.4)	137 (56.1)	66 (53.2)	71 (57.7)	66 (53.7)
TEAE, by severity								
Mild	67 (26.9)	36 (28.3)	41 (33.3)	48 (38.4)	91 (37.3)	37 (29.8)	47 (38.2)	44 (35.8)
Moderate	61 (24.5)	28 (22.0)	27 (22.0)	23 (18.4)	37 (15.2)	23 (18.5)	19 (15.4)	19 (15.4)
Severe	7 (2.8)	5 (3.9)	3 (2.4)	2 (1.6)	9 (3.7)	6 (4.8)	5 (4.1)	3 (2.4)
Serious adverse events	6 (2.4)	1 (0.8)	0	2 (1.6)	9 (3.7)	9 (7.3)	3 (2.4)	1 (0.8)
AEs leading to discontinuation	4 (1.6)	2 (1.6)	1 (0.8)	1 (0.8)	2 (0.8)	7 (5.6)	3 (2.4)	2 (1.6)
MACE ^a	0	0	0	0	0	0	0	0
Death	0	0	0	0	0	0	0	0
Infectious AEs								
Nasopharyngitis	26 (10.4)	22 (17.3)	12 (9.8)	12 (9.6)	30 (12.3)	13 (10.5)	16 (13.0)	10 (8.1)
Upper respiratory tract infection	6 (2.4)	1 (0.8)	3 (2.4)	4 (3.2)	5 (2.0)	6 (4.8)	5 (4.1)	4 (3.3)
Herpes								
Herpes simplex ^b	3 (1.2)	7 (5.5)	4 (3.3)	9 (7.2)	11 (4.5)	6 (4.8)	7 (5.7)	5 (4.1)
Herpes zoster ^c	1 case				2 cases			
Urinary tract infection	4 (1.6)	1 (0.8)	2 (1.6)	4 (3.2)	3 (1.2)	0	0	2 (1.6)
Gastroenteritis	1 (0.4)	1 (0.8)	0	3 (2.4)	3 (1.2)	0	0	0
Rhinitis	2 (0.8)	1 (0.8)	0	3 (2.4)	1 (0.4)	2 (1.6)	0	0
Skin Infection requiring antibiotic treatment	11 (4.4)	1 (0.8)	6 (4.9)	4 (3.2)	19 (7.8)	6 (4.8)	9 (7.3)	6 (4.9)

Non-infectious AEs								
Headache	16 (6.4)	7 (5.5)	14 (11.4)	10 (8.0)	5 (2.0)	6 (4.8)	9 (7.3)	11 (8.9)
Blood CPK increased	2 (0.8)	1 (0.8)	1 (0.8)	4 (3.2)	1 (0.4)	4 (3.2)	1(0.8)	7 (5.7)
Diarrhoea	7 (2.8)	9 (7.1)	0	4 (3.2)	4 (1.6)	2 (1.6)	3 (2.4)	3 (2.4)
Abdominal pain, upper	1 (0.4)	1 (0.8)	2 (1.6)	3 (2.4)	7 (2.9)	3 (2.4)	4 (3.3)	4 (3.3)
Ocular AEs ^d								
Conjunctivitis/Keratitis	4 (1.6)	1 (0.8)	2 (1.6)	1 (0.8)	2 (0.8)	6 (2.8)	2 (1.6)	0

AE, adverse event; Bari, baricitinib; CPK, creatine phosphokinase; MACE, major adverse cardiovascular event; N, number of subjects in the safety population; n, number of subjects in the specified category; PBO, placebo; TEAE, treatment-emergent adverse event.

Events occurring at a $\geq 2\%$ frequency in any treatment group. Data reported as n (%) unless otherwise noted.

^aA major adverse cardiovascular event was defined as cardiovascular death, myocardial infarction, or stroke, as adjudicated by an independent clinical event committee.

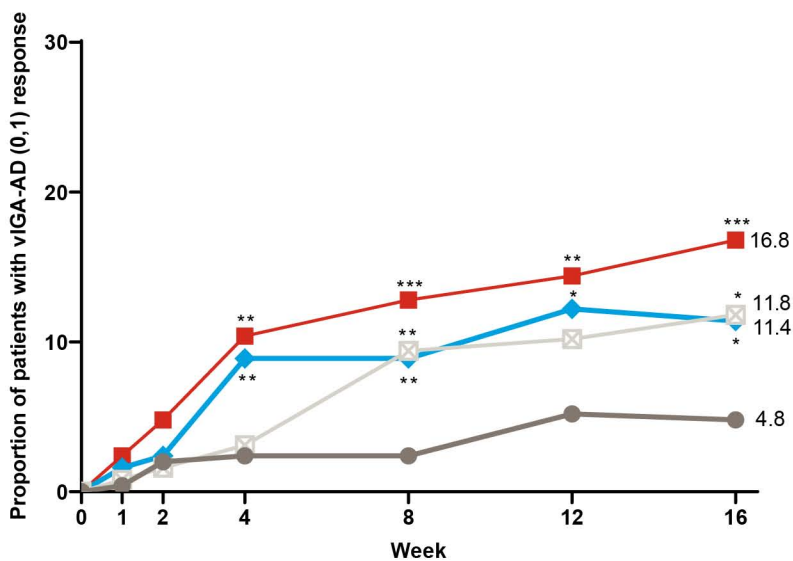
^bHerpes simplex include all Herpes simplex related terms and not events occurring at a $\geq 2\%$ frequency in any treatment group.

^cHerpes zoster cases are not yet unblinded to investigators and treatment groups cannot be reported.

^dIdentified using conjunctival disorders SMQ20000175.

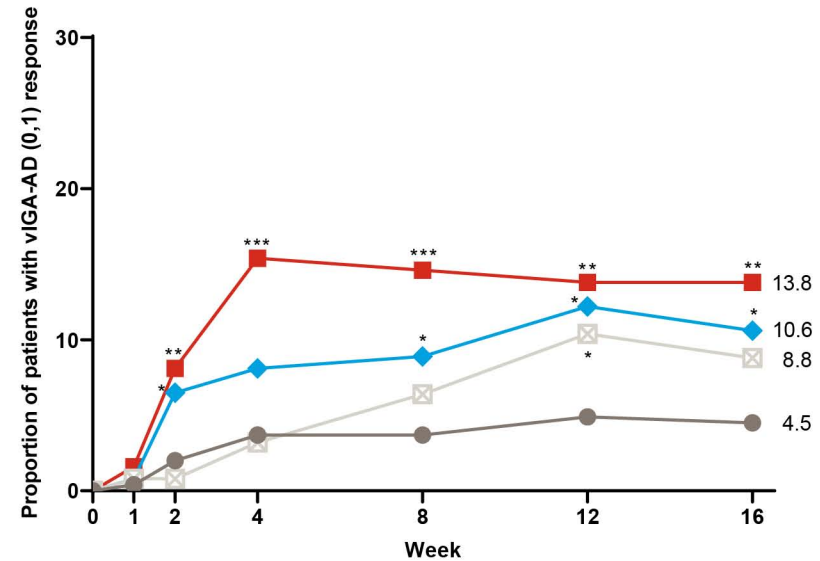
BREEZE-AD1

(a) Monotherapy^a

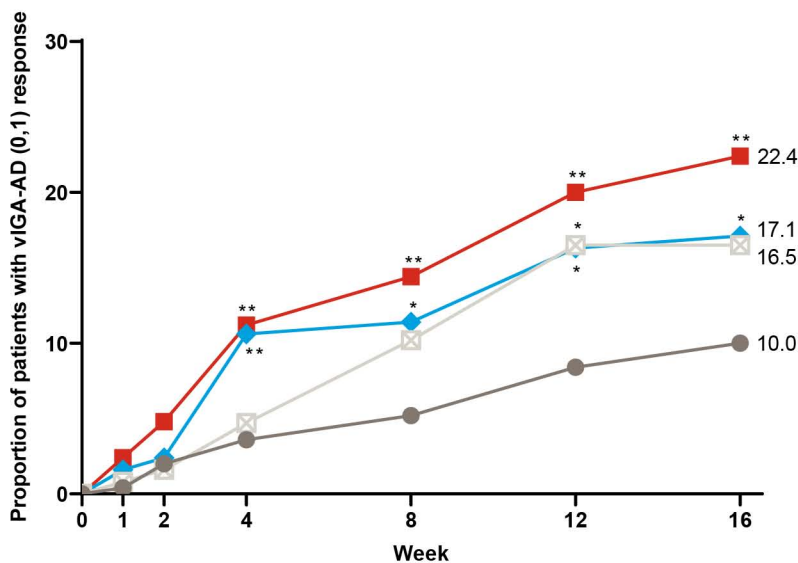


BREEZE-AD2

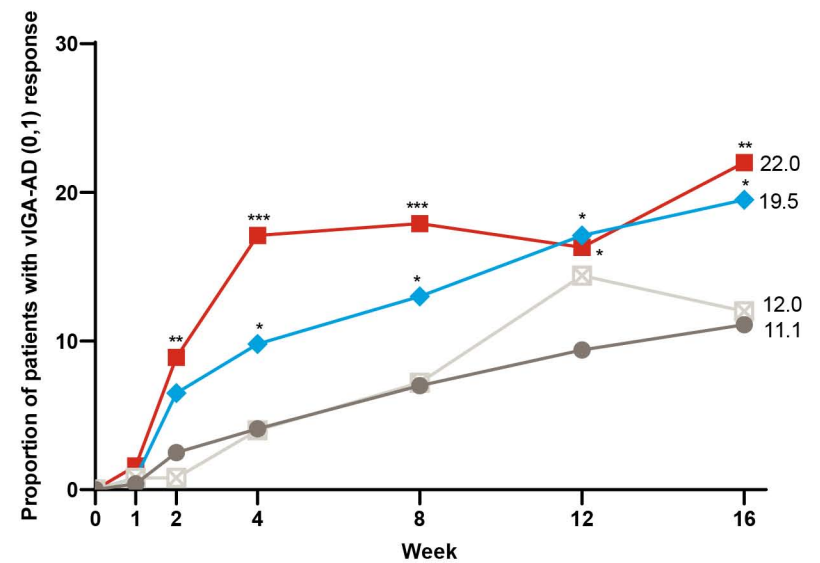
(b) Monotherapy^a



(c) With TCS Rescue^b



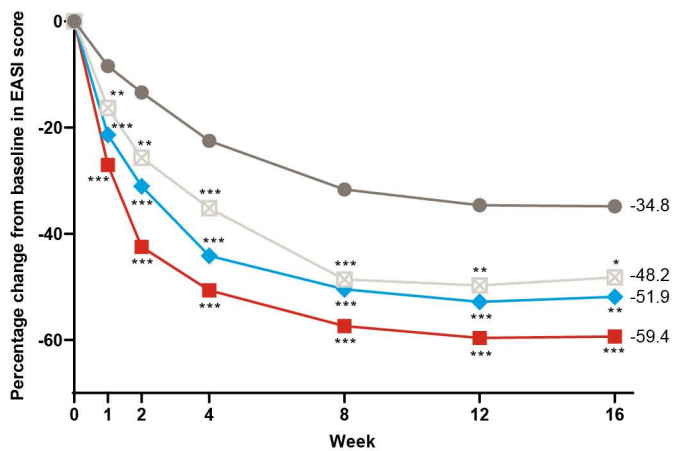
(d) With TCS Rescue^b



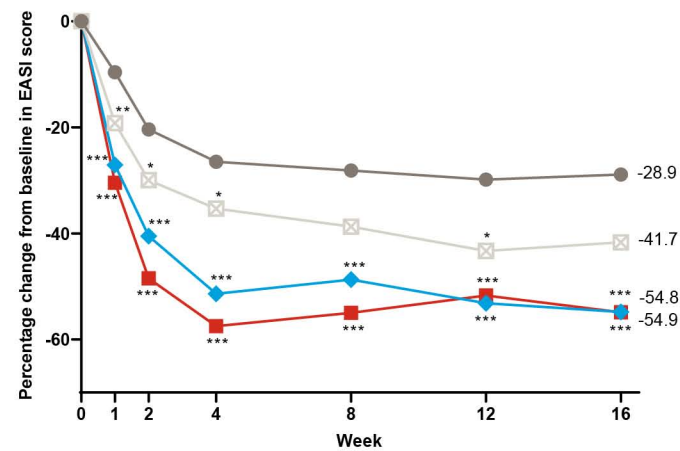
- Placebo
- ⊠ Baricitinib 1-mg
- ◆ Baricitinib 2-mg
- Baricitinib 4-mg

BREEZE-AD1

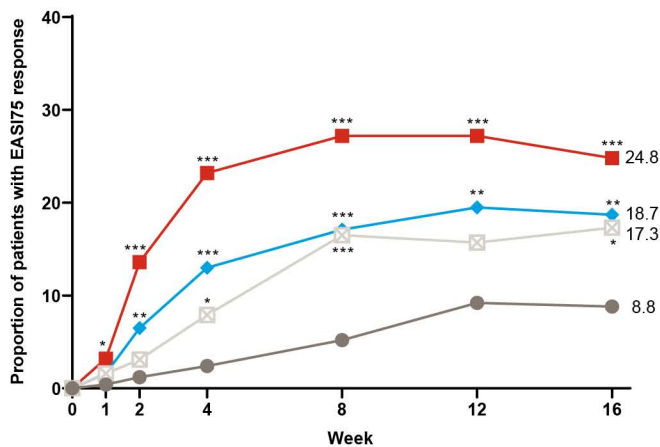
(a) Monotherapy^a



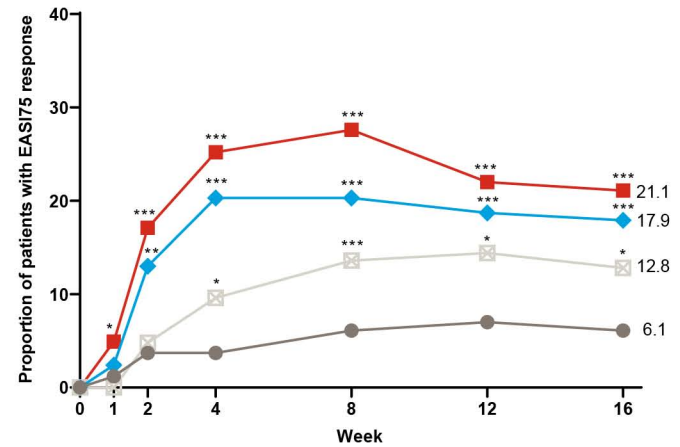
(b) Monotherapy^a



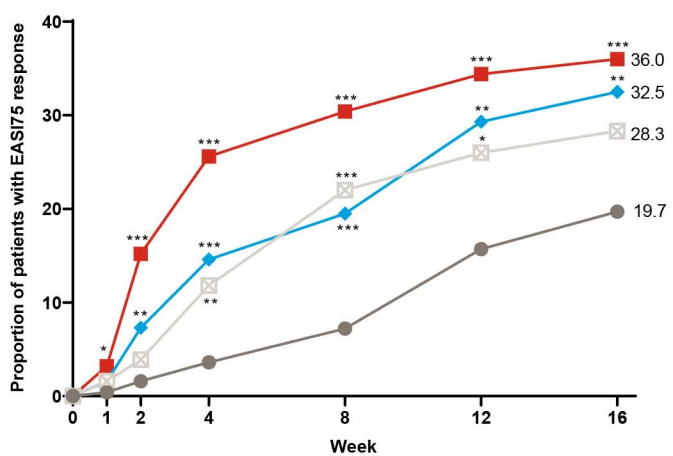
(c) Monotherapy^a



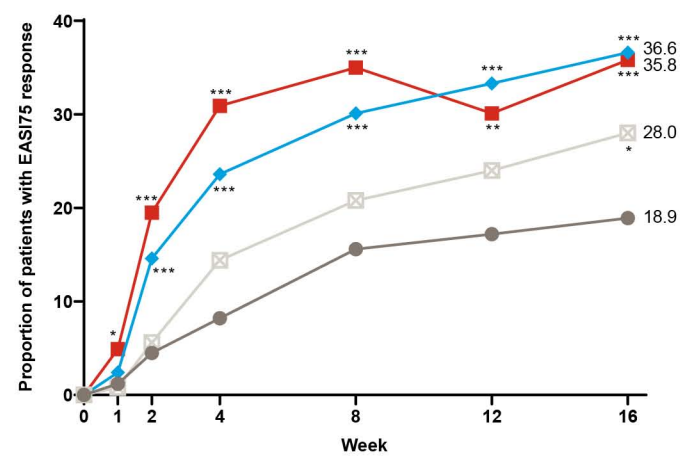
(d) Monotherapy^a



(e) With TCS Rescue^b



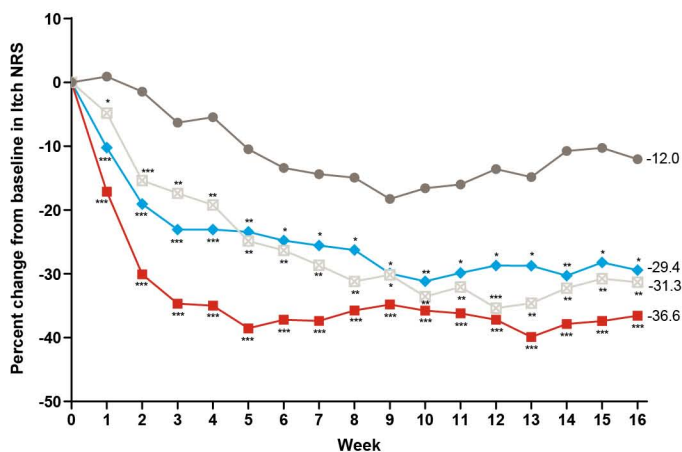
(f) With TCS Rescue^b



● Placebo
 □ Baricitinib 1-mg
 ◆ Baricitinib 2-mg
 ■ Baricitinib 4-mg

BREEZE-AD1

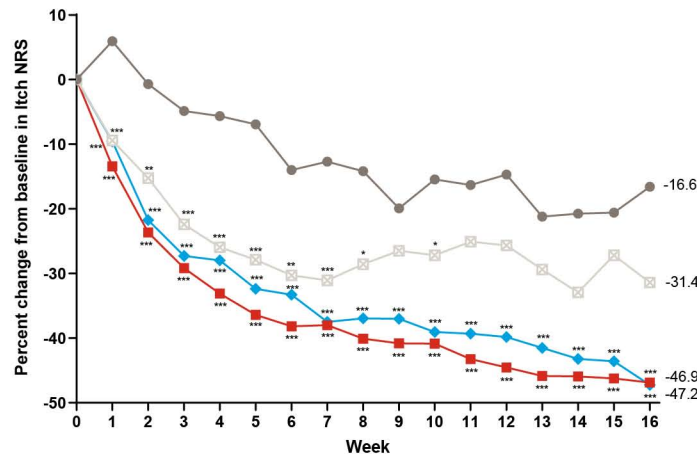
(a) Monotherapy^a



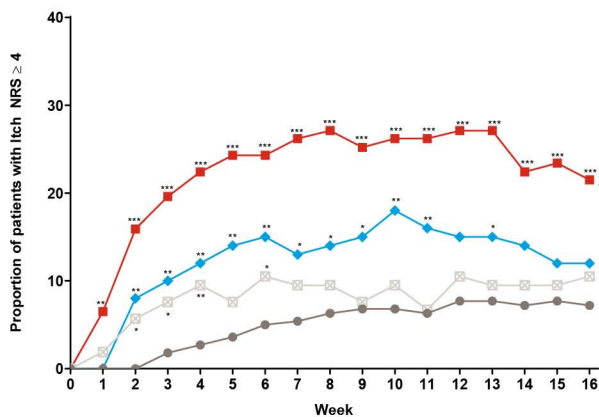
BREEZE-AD2



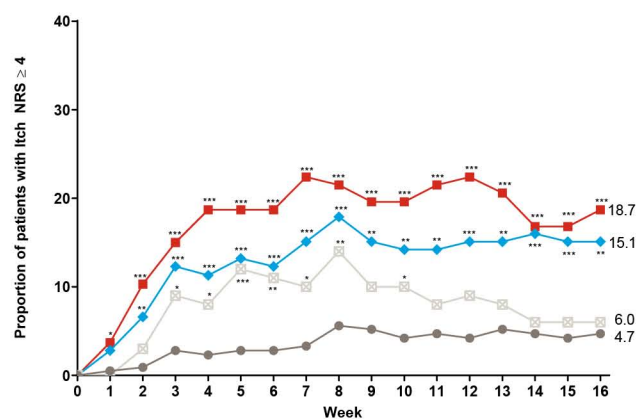
(b) Monotherapy^a



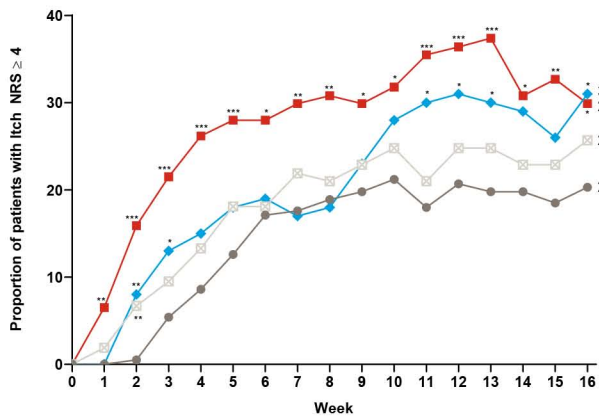
(c) Monotherapy^a



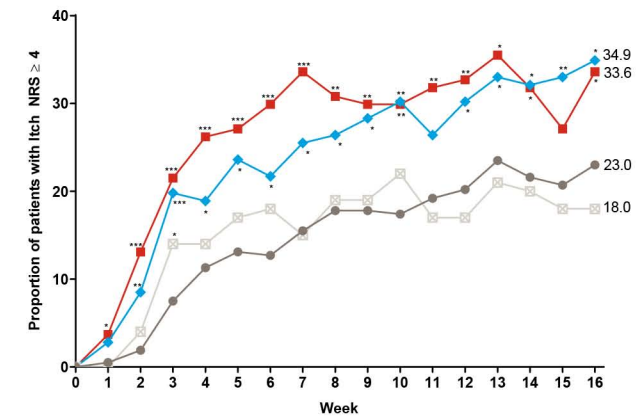
(d) Monotherapy^a



(e) With TCS Rescue^b

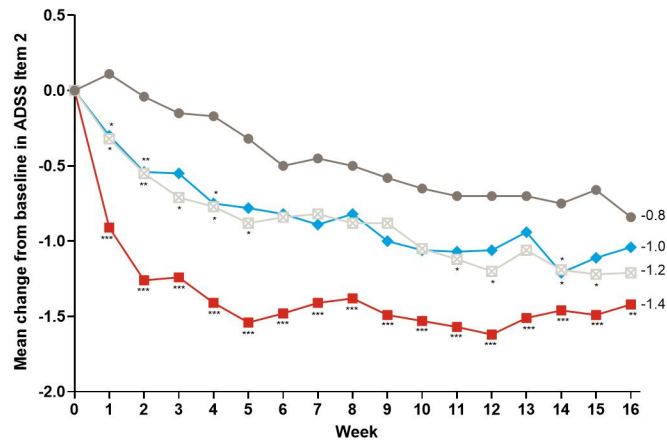


(f) With TCS Rescue^b

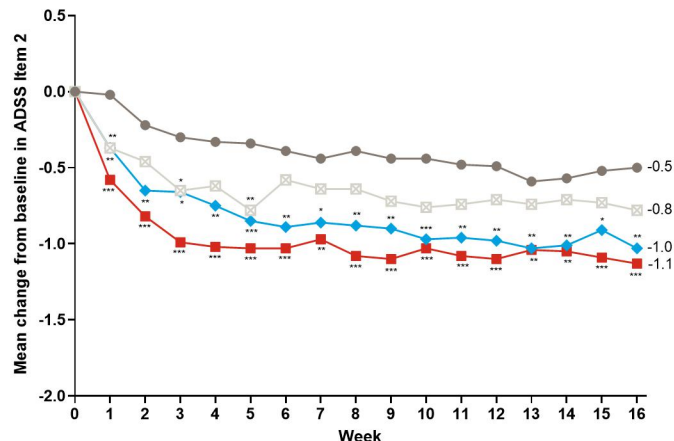


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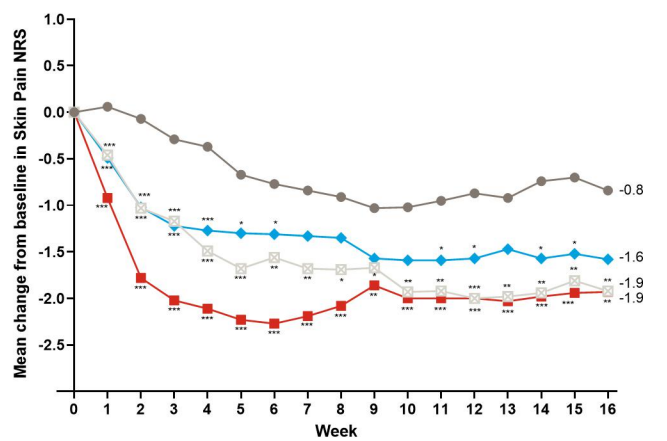


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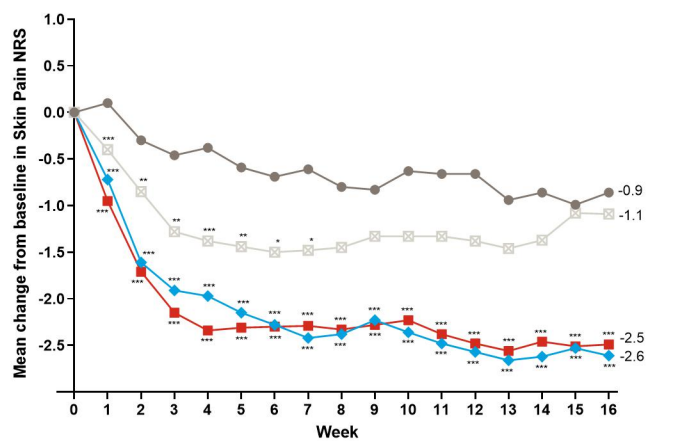


Skin Pain NRS

(c)

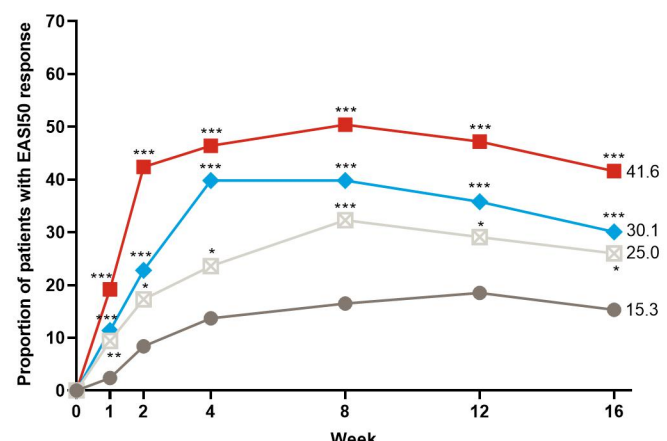


(d)

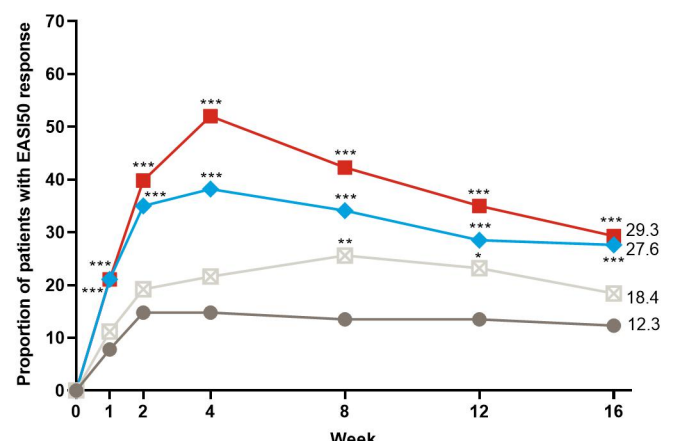


EASI50

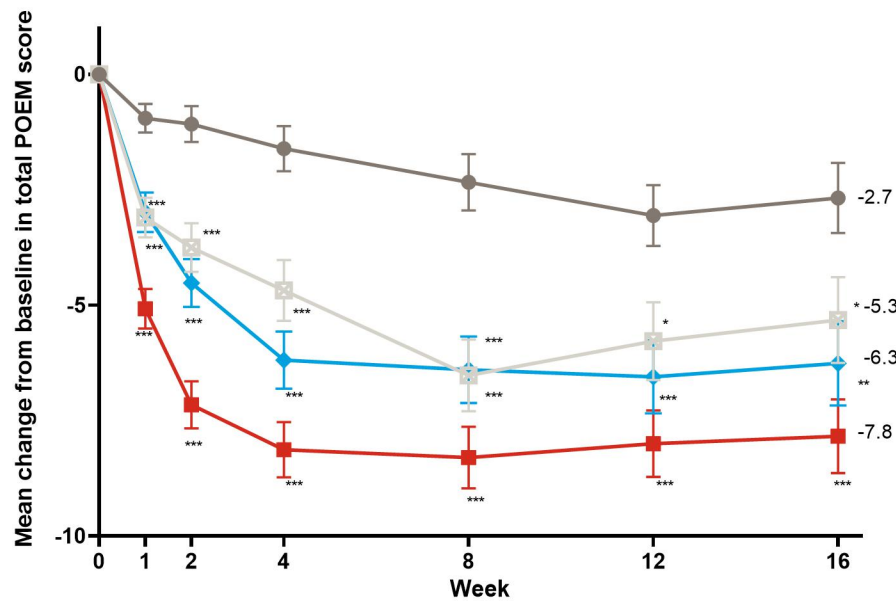
(e)



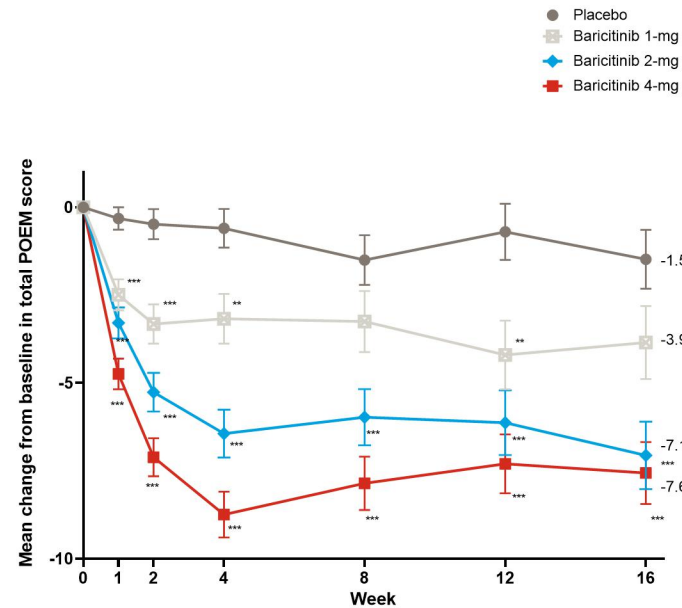
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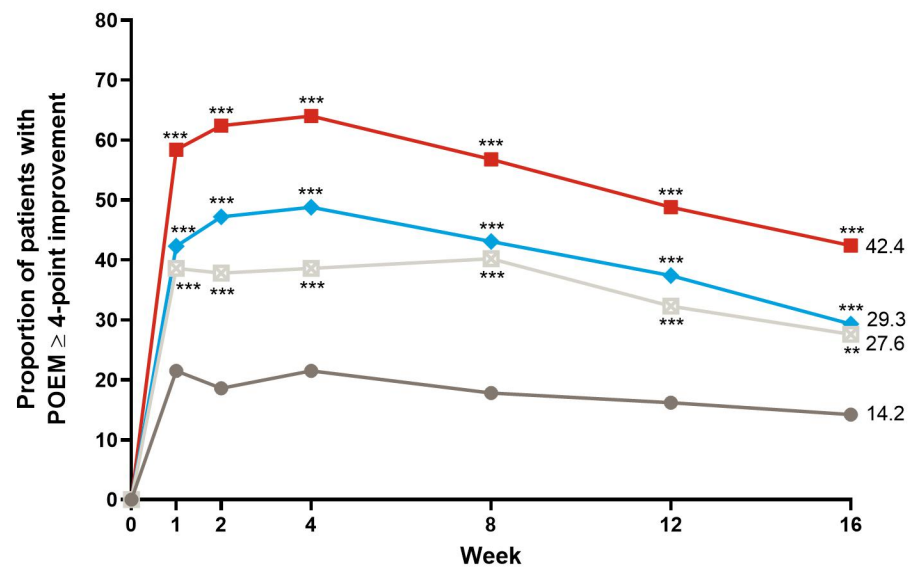
(a)



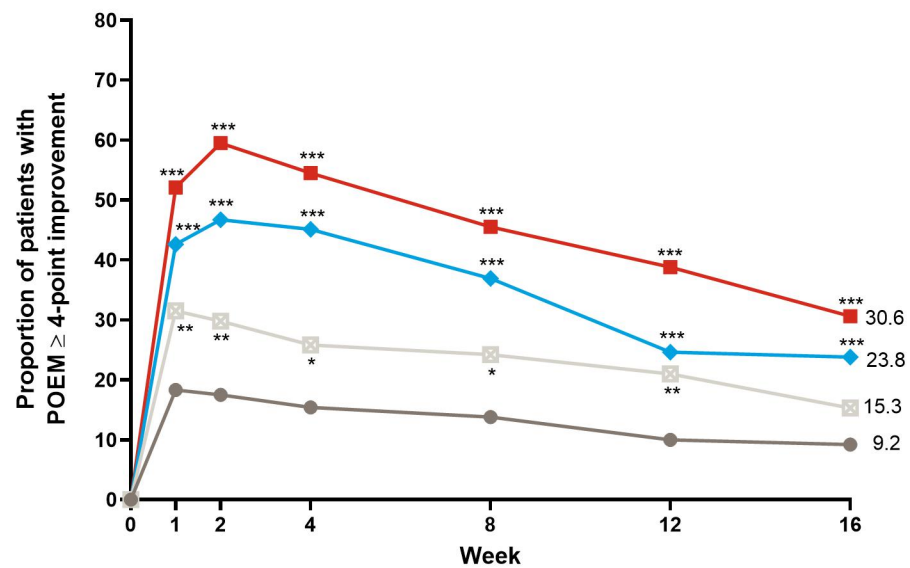
(b)



(c)



(d)



Supplemental Material

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: *Baricitinib in Patients with Moderate-to-Severe Atopic Dermatitis and Inadequate Response to Topical Corticosteroids: Results from Two Randomised Monotherapy Phase III Trials*

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Table S1. List of study investigators and sites for BREEZE-AD1 and BREEZE-AD2*

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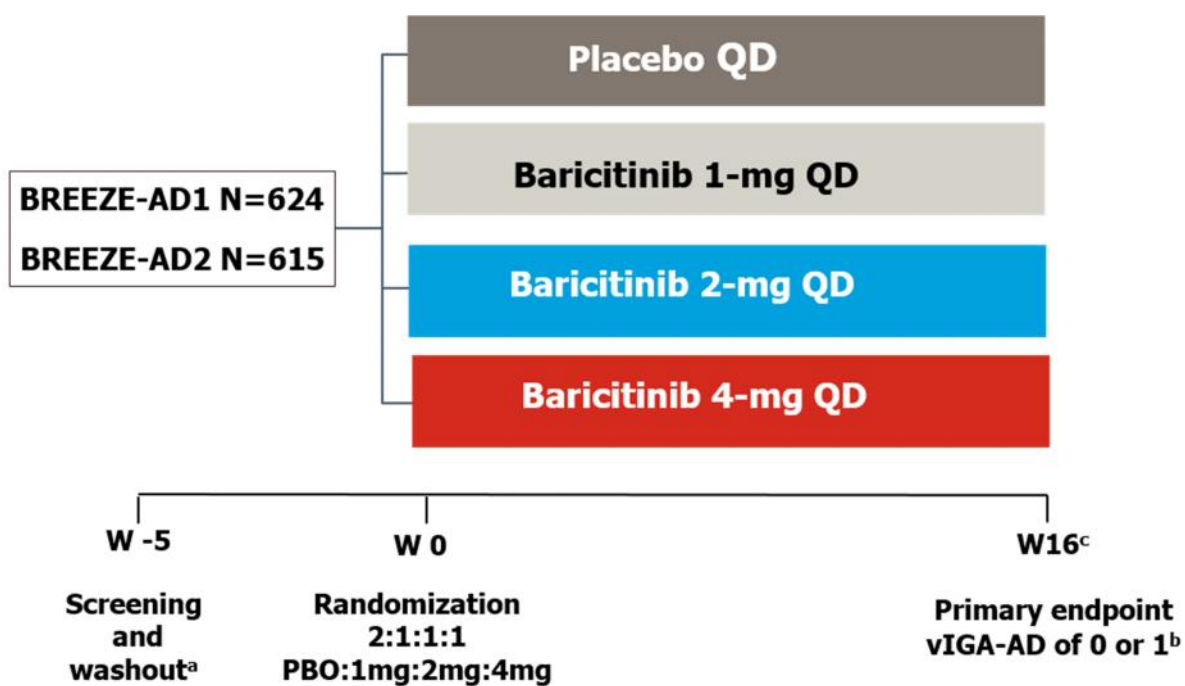
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Figure S1. BREEZE-AD1 and BREEZE-AD2 study design



AD, Atopic dermatitis; PBO, Placebo; QD, once-daily; vIGA-AD, Validated Investigator's Global Assessment of Atopic Dermatitis; W, Week.

^a Applicable to patients taking topical treatments (excluding emollients) or systemic treatments for AD at the time of screening; ^b Proportion of patients achieving vIGA-AD (0, 1) with a ≥ 2 -point improvement; ^c Patients who do not enroll into the ongoing, long-term extension study BREEZE-AD3 will complete post-treatment period (28 days).

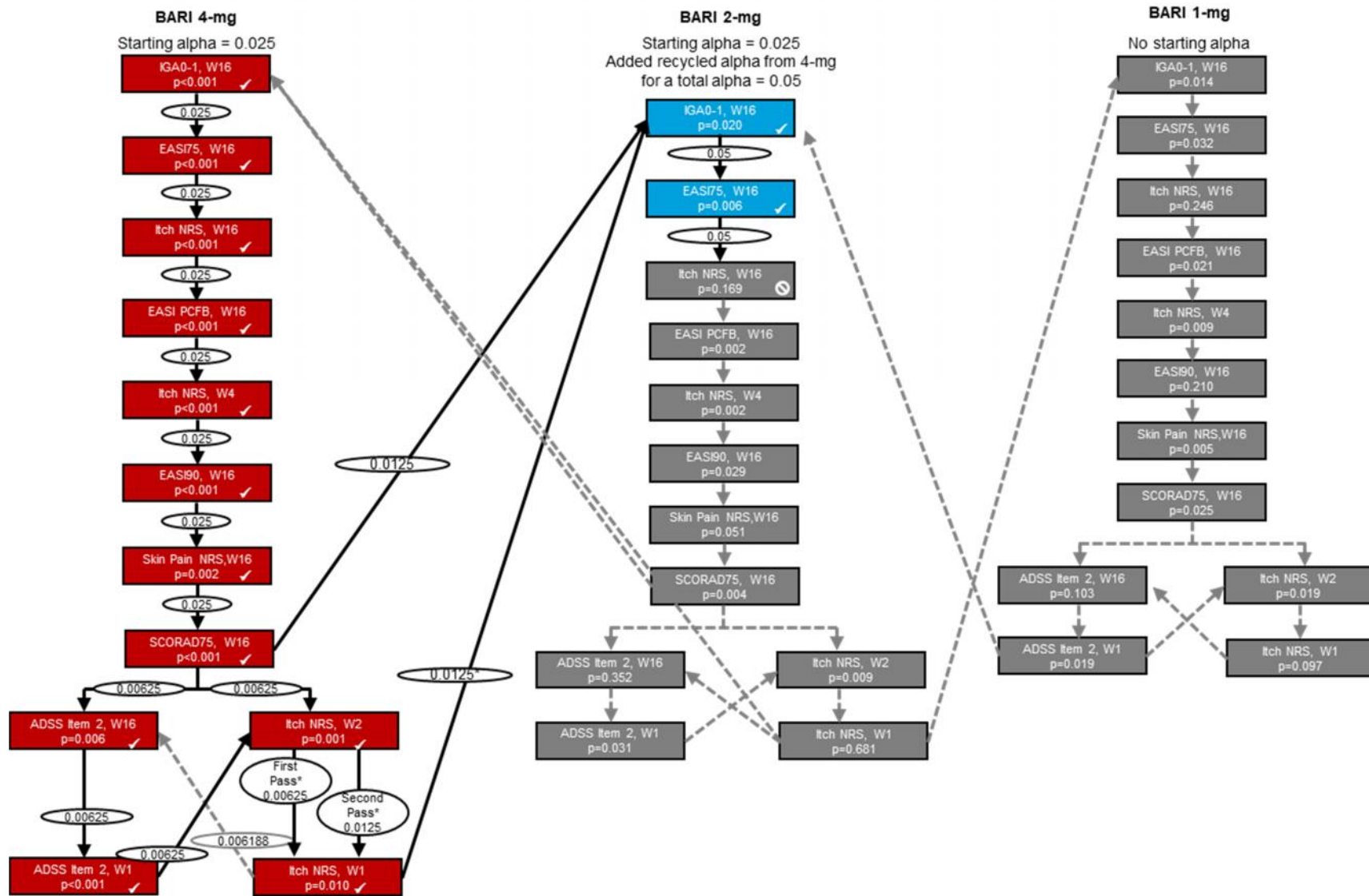


Figure S2. Results for graphical multiple-testing procedure in BREEZE-AD1

ADSS, Atopic Dermatitis Sleep Scale; BARI, baricitinib; EASI, Eczema Area and Severity Index; vIGA, Validated Investigator's Global Assessment; NRS, Numeric Rating Scale, SCORAD, SCORing Atopic Dermatitis; PCFB, percent change from baseline; W, week.

Numbers in ovals indicate testing alpha for the endpoint indicated by the accompanying arrow. Checkmarks indicate the endpoint achieved significance and the box subsequently displayed in red or blue.. Stop symbol indicates the endpoint did not achieve significance and further testing within that dose group was terminated..

Grey dashed arrows indicate alpha would have been passed along that route had one of the tests in that route had failed.

For 4-mg this occurred because the ADSS Item 2 Week 16 endpoint was significant on the first pass, so there was no need for a second pass with the additional recycled alpha.

* Itch NRS Week 1 passed on the second pass, after the alpha from ADSS Item 2 Week 1 was recycled to Itch NRS Week 2 for a total recycled alpha of 0.0125. This alpha was then recycled to the 2-mg dose.

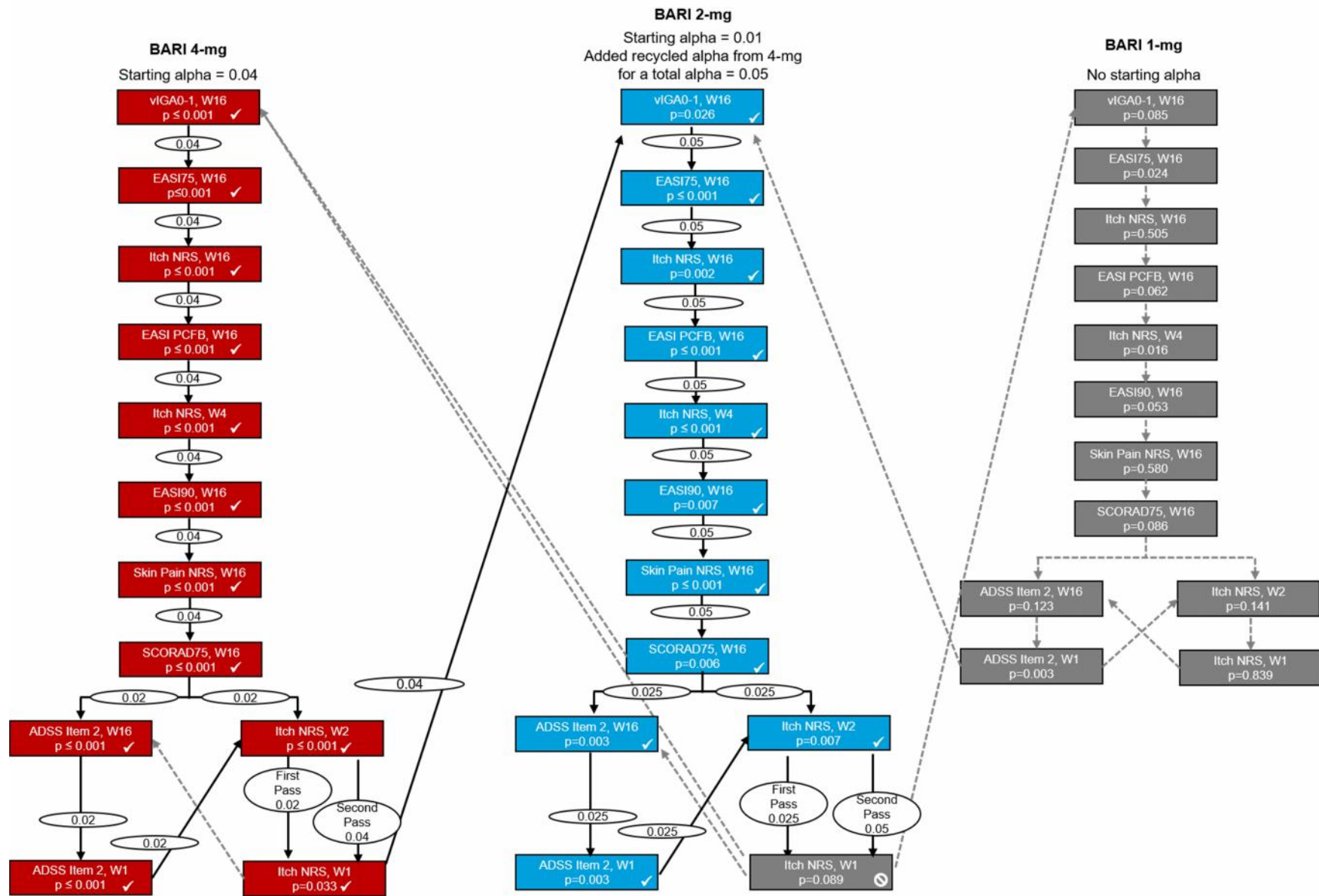
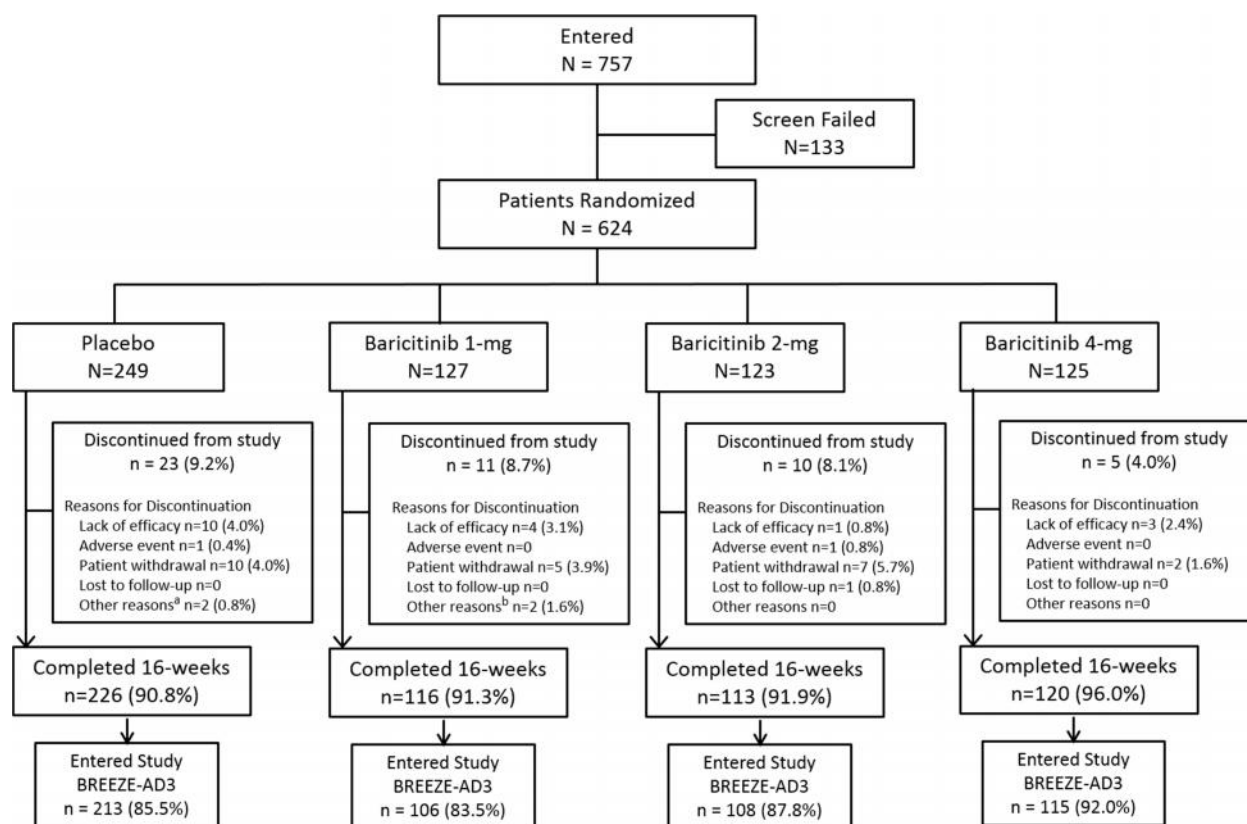


Figure S3. Results for graphical multiple-testing procedure in BREEZE-AD2

ADSS, Atopic Dermatitis Sleep Scale; BARI, baricitinib; EASI, Eczema Area and Severity Index; vIGA, Validated Investigator's Global Assessment; NRS, Numeric Rating Scale, SCORAD, SCORing Atopic Dermatitis; PCFB, percent change from baseline; W, week.

Numbers in ovals indicate testing alpha for the endpoint indicated by the accompanying arrow. Checkmarks indicate the endpoint achieved significance and the box subsequently displayed in red or blue. Stop symbol indicates the endpoint did not achieve significance and further testing within that dose group was terminated. Grey dashed arrows indicate alpha would have been passed along that route had one of the tests in that route had failed. Since ADSS Item 2 for Week 16 and Week 1 were significant after initial tests, the alpha from itch NRS Week 1 was not passed through that testing route.

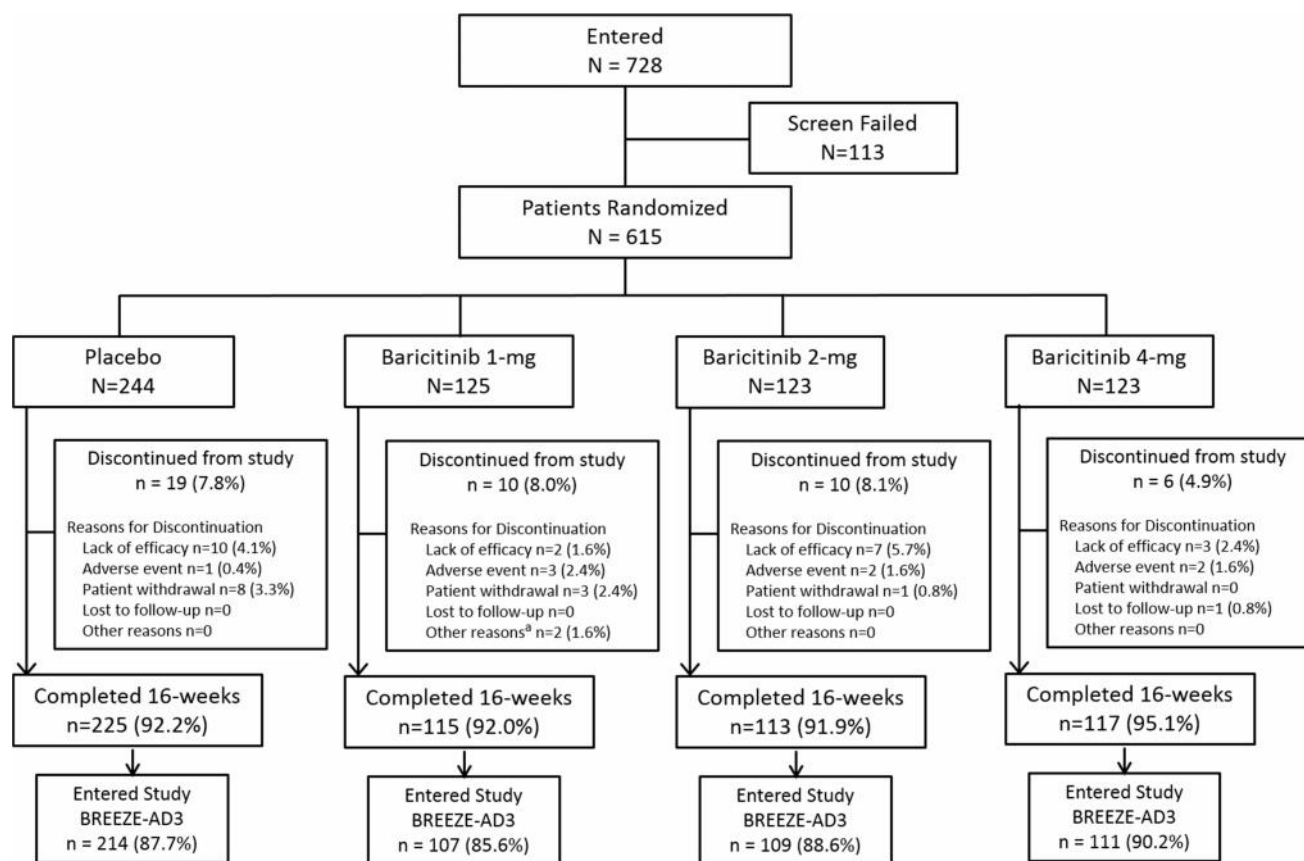
* Itch NRS Week 1 was significant on the second test after the alphas from ADSS Item 2 Week 1 (0.02) and Itch NRS week 2 (0.02) were combined and passed to it for a total testing alpha of 0.04. Subsequently this alpha (0.04) was passed to the 2-mg dose resulting in an initial alpha of 0.05.

Figure S4. Patient disposition in BREEZE-AD1 through 16 weeks.

^a For placebo the other reasons included: physician decision, n=1; participant decision, n=1.

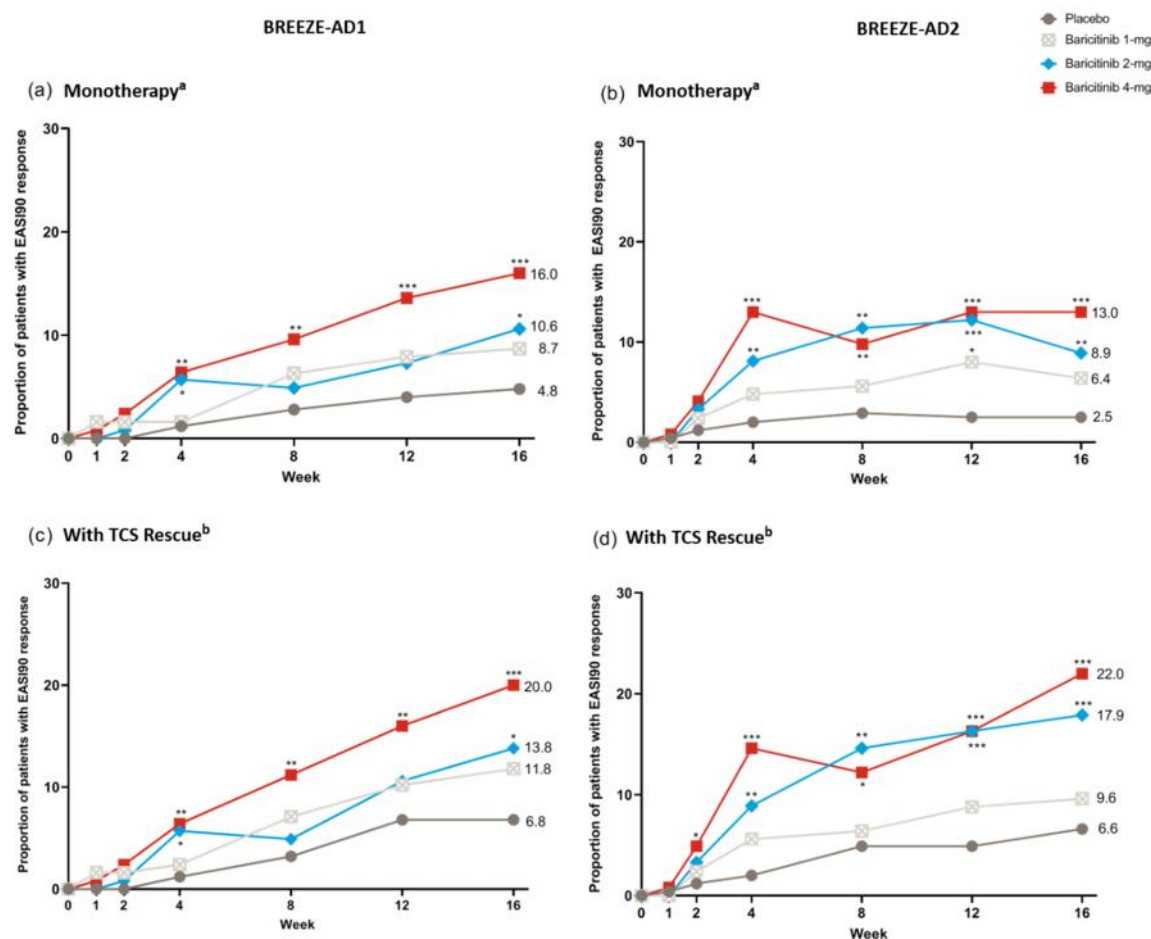
^b For baricitinib 1 mg the other reasons included: pregnancy, n=1; participant did not meet inclusion/exclusion criteria, n=1.

Figure S5. Patient disposition in BREEZE-AD2 through 16 weeks.



^a For baricitinib 1 mg the other reasons included: pregnancy, n=1; inability to obtain laboratory samples, n=1.

Figure S6. Proportion of patients achieving at least 90% improvement in EASI score (EASI90) in BREEZE-AD1 (a, c) and BREEZE-AD2 (b, d).



EASI, Eczema Area and Severity Index; TCS, topical corticosteroids.

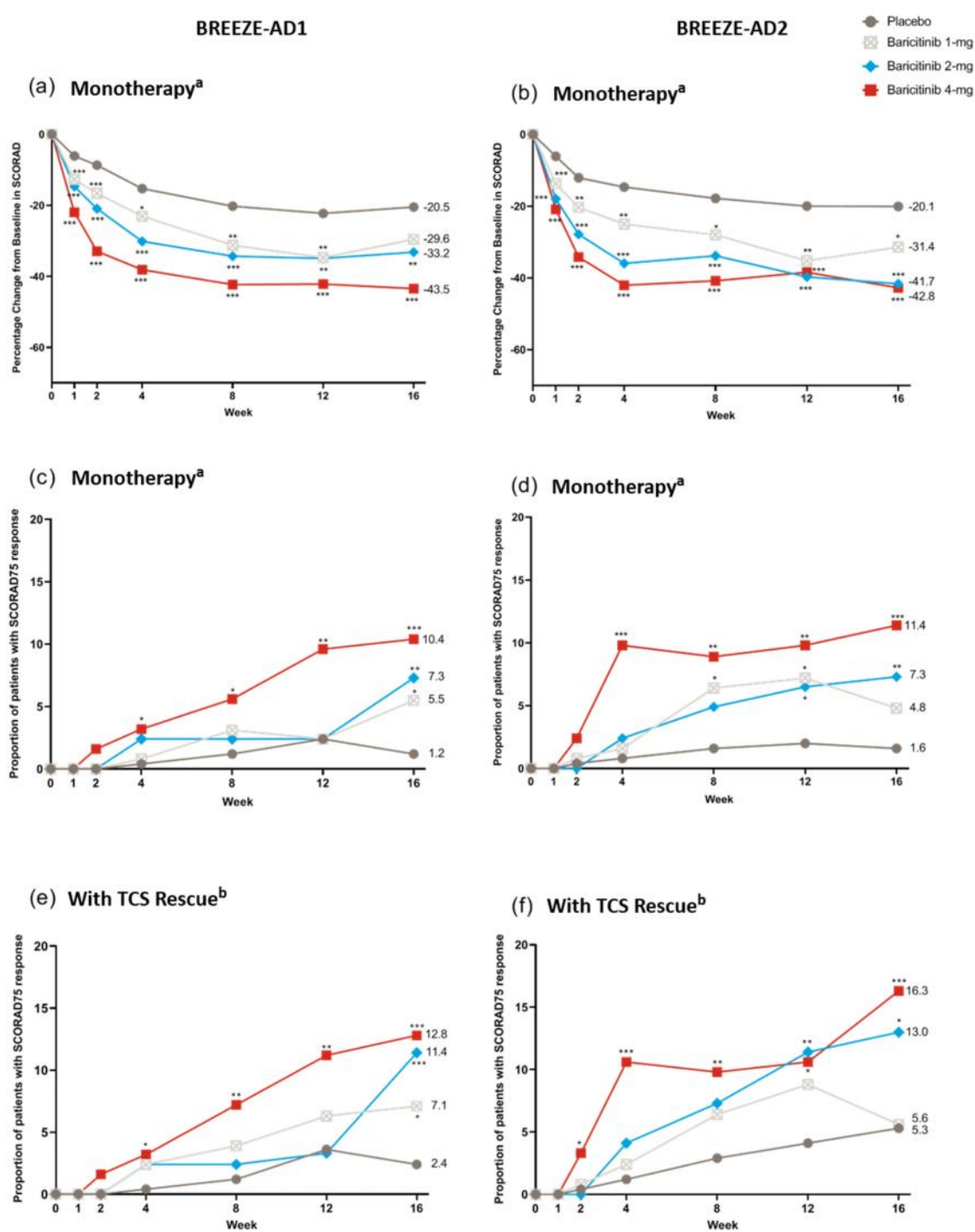
^aData were censored after rescue or after permanent study drug discontinuation and imputed using nonresponder imputation.

^bIncludes observed values up to permanent study drug discontinuation.

* $P \leq 0.05$, ** $P \leq 0.01$ and *** $P \leq 0.001$ for analyses comparing baricitinib with placebo

Figure S7. Percent change from baseline SCORAD index in BREEZE-AD1 (a) and BREEZE-AD2 (b).

Proportion of patients with 75% improvement in SCORAD (SCORAD75) response in BREEZE-AD1 (c, e) and BREEZE-AD2 (d, f).



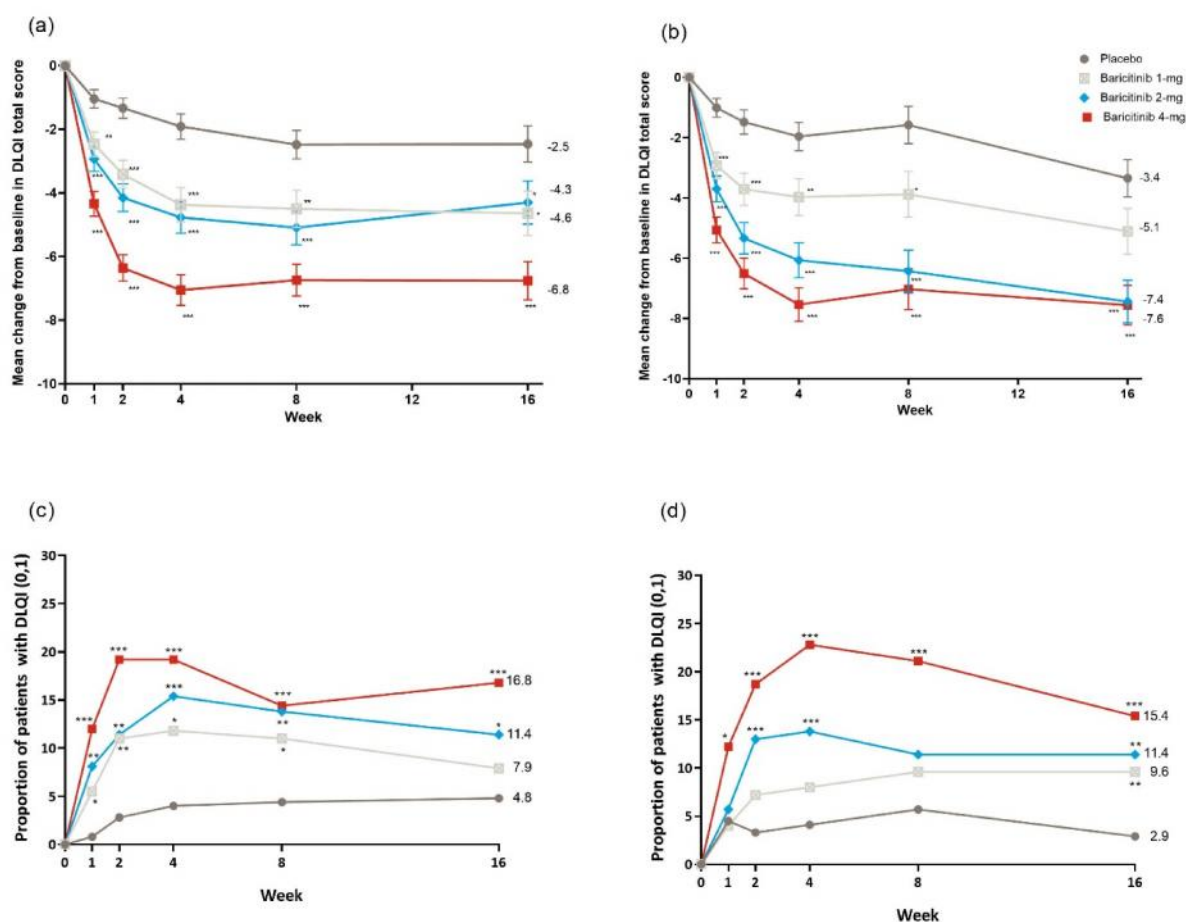
SCORAD, SCORing Atopic Dermatitis; TCS, topical corticosteroids.

^a Data collected after rescue therapy or after permanent study drug discontinuation are censored and set to missing. For continuous endpoints, LS means are from MMRM analyses, which incorporates multiple imputation for missing data. For categorical endpoints, a nonresponder imputation was applied at censoring

^bIncludes observed values up to permanent study drug discontinuation.

* $P \leq 0.05$, ** $P \leq 0.01$ and *** $P \leq 0.001$ for analyses comparing baricitinib with placebo.

Figure S8. Mean change from baseline and standard error in DLQI and proportion of patients with DLQI scores of 0 or 1 in BREEZE-AD1 (a, c) and BREEZE-AD2 (b, d), respectively.

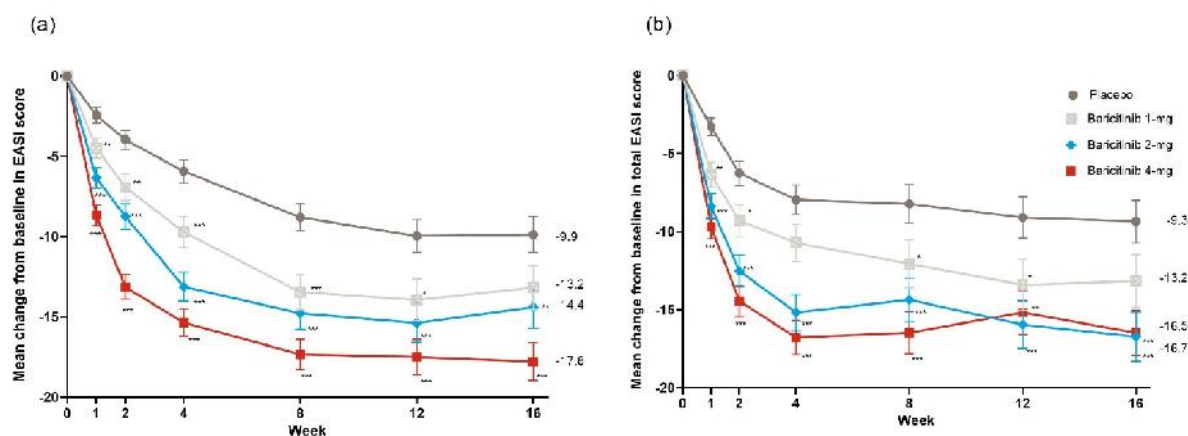


DLQI, Dermatology Life Quality Index.

Data collected after rescue therapy or after permanent study drug discontinuation are censored and set to missing. For continuous endpoints, LS means are from MMRM analyses, which incorporates multiple imputation for missing data. For categorical endpoints, a nonresponder imputation was applied at censoring.

* $P \leq 0.05$, ** $P \leq 0.01$ and *** $P \leq 0.001$ for analyses comparing baricitinib with placebo

Figure S9. Mean change from baseline and standard error in total EASI score in BREEZE-AD1 (a) and BREEZE-AD2 (b).

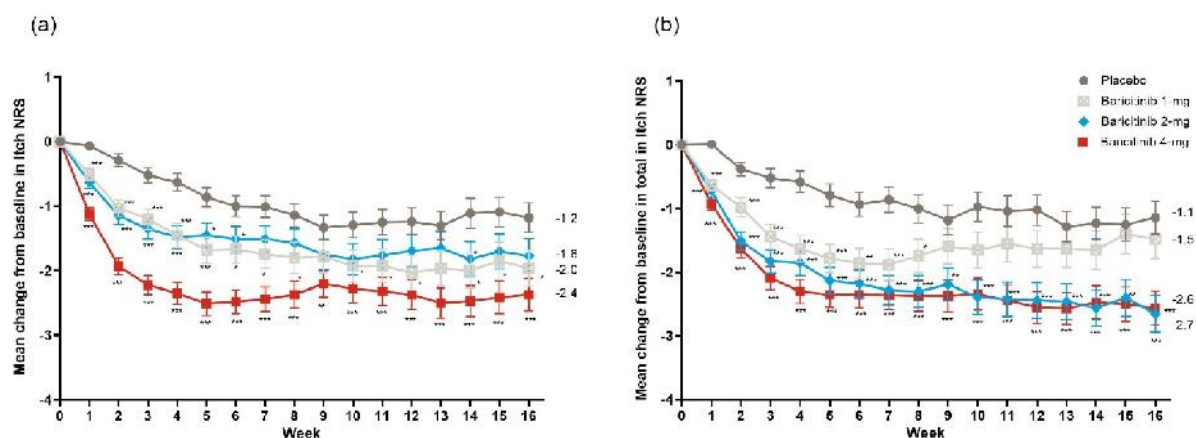


EASI, Eczema Area and Severity Index.

Data reported from monotherapy analysis. Data collected after rescue therapy or after permanent study drug discontinuation are censored and set to missing. For continuous endpoints, LS means are from MMRM analyses, which incorporates multiple imputation for missing data.

* $p \leq 0.05$, ** $p \leq 0.01$ and *** $p \leq 0.001$ for analyses comparing baricitinib with placebo.

Figure S10. Mean change from baseline and standard error in the itch numeric rating scale in BREEZE-AD1 (a) and BREEZE-AD2 (b).



NRS, numeric rating scale.

Data reported from monotherapy analysis. Data collected after rescue therapy or after permanent study drug discontinuation are censored and set to missing. For continuous endpoints, LS means are from MMRM analyses, which incorporates multiple imputation for missing data.

* $P \leq 0.05$, ** $P \leq 0.01$ and *** $P \leq 0.001$ for analyses comparing baricitinib with placebo.

Table S2. Response rates and NNT in BREEZE-AD1/BREEZE-AD2 at Week 16

	Response rates (%)			Numbers needed to treat	
	PBO	Bari 2-mg	Bari 4-mg	Bari 2-mg	Bari 4-mg
vIGA (0, 1)	4.7	11.0	15.3	16	10
EASI 75	7.5	18.3	23.0	10	7
Itch 4-point improvement	6.0	13.6	20.1	14	8

Bari, baricitinib; EASI75, 75% reduction in Eczema Area and Severity Index; NNT, numbers needed to treat; PBO, placebo; vIGA, Validated Investigator's Global Assessment

Rates and NNT evaluated from combined BREEZE-AD1 and BREEZE-AD2 monotherapy data at Week 16.

Table S3. Summary of additional secondary endpoints at Week 16

	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)
vIGA-AD of 0, % (n)	0.8 (2)	1.6 (2)	2.4 (3)	1.6 (2)	1.6 (4)	2.4 (3)	4.1 (5)	4.1 (5)
95% CI	(0.2, 2.9)	(0.4, 5.6)	(0.8, 6.9)	(0.4, 5.6)	(0.6, 4.1)	(0.8, 6.8)	(1.7, 9.2)	(1.7, 9.2)
p-value vs. placebo		0.424	0.182	0.441		0.528	0.142	0.123
OR (95% CI) vs. placebo		2.0 (0.4, 10.6)	2.9 (0.6, 13.8)	1.9 (0.4, 10.4)		1.6 (0.4, 6.3)	2.6 (0.7, 9.0)	2.7 (0.8, 9.4)
SCORAD90, % (n)	0.8 (2)	0.8 (1)	2.4 (3)	2.4 (3)	1.2 (3)	3.2 (4)	4.1 (5)	4.9 (6)
95% CI	(0.2, 2.9)	(0.1, 4.3)	(0.8, 6.9)	(0.8, 6.8)	(0.4, 3.6)	(1.3, 7.9)	(1.7, 9.2)	(2.3, 10.2)
p-value vs. placebo		0.874	0.176	0.201		0.193	0.042	0.044
OR (95% CI) vs. placebo		1.2 (0.2, 7.8)	2.9 (0.6, 13.4)	2.7 (0.6, 12.7)		2.6 (0.6, 10.5)	4.1 (1.1, 16.0)	3.9 (1.0, 14.6)
Change from baseline in SCORAD, LSM (SE)	-13.5 (2.0)	-18.9 (2.5)	-21.5 (2.4)	-28.3 (2.1)	-13.4 (2.3)	-20.2 (2.8)	-27.8 (2.6)	-27.5 (2.4)
LSM difference from placebo, (SE)		-5.3 (3.2)	-8.0 (3.1)	-14.8 (2.9)		-6.9 (3.6)	-14.5 (3.5)	-14.1 (3.3)
LSM Difference from placebo, 95% CI		(-11.6, 0.9)	(-14.0, -1.9)	(-20.5, -9.1)		(-14.0, 0.3)	(-21.3, -7.6)	(-20.7, -7.6)
p-value vs. placebo		0.093	0.010	<0.001		0.059	<0.001	<0.001
Change in BSA, LSM (SE)	-14.8 (1.8)	-20.8 (2.3)	-20.1 (2.2)	-26.0 (1.9)	-12.8 (2.1)	-19.0 (2.5)	-22.1 (2.4)	-24.0 (2.2)
LSM difference from placebo, (SE)		-6.0 (2.9)	-5.3 (2.8)	-11.2 (2.6)		-6.2 (3.2)	-9.3 (3.1)	-11.12 (3.0)
LSM Difference from placebo, 95% CI		(-11.7, -0.3)	(-10.9, 0.2)	(-16.3, -6.0)		(-12.5, 0.2)	(-15.4, -3.2)	(-17.0, -5.3)
p-value vs. placebo		0.039	0.058	<0.001		0.058	0.003	<0.001

Bari, baricitinib; BSA, body surface area; LSM, least squares mean; PBO, placebo; SCORAD, SCORing Atopic Dermatitis; SE, standard error; vIGA-AD, validated Investigator's Global Assessment of Atopic Dermatitis.

Data reported from monotherapy analysis. Data collected after rescue therapy or after permanent study drug discontinuation are censored and set to missing. For continuous endpoints, LS means are from MMRM analyses, which incorporates multiple imputation for missing data. For categorical endpoints, a nonresponder imputation was applied at censoring

Table S4. Cumulative rescue rates at key time points in BREEZE-AD1 and BREEZE-AD2

Rescue time points	BREEZE-AD1				BREEZE-AD2			
	PBO	Bari 1-mg	Bari 2-mg	Bari 4-mg	PBO	Bari 1-mg	Bari 2-mg	Bari 4-mg
	(N=249)	(N=127)	(N=123)	(N=125)	(N=244)	(N=125)	(N=123)	(N=123)
Week 2	100 (40.2)	46 (36.2)	30 (24.4)	15 (12.0)	132 (54.1)	49 (39.2)	43 (35.0)	35 (28.5)
Week 4	132 (53.0)	54 (42.5)	40 (32.5)	25 (20.0)	159 (65.2)	65 (52.0)	54 (43.9)	45 (36.6)
Week 12	161 (64.7)	69 (54.3)	64 (52.0)	51 (40.8)	186 (76.2)	84 (67.2)	81 (65.9)	70 (56.9)
Week 16	166 (66.7)	69 (54.3)	66 (53.7)	51 (40.8)	187 (76.6)	85 (68.0)	81 (65.9)	72 (58.5)

Bari, baricitinib; PBO, placebo.

Data reported as n (%)

Table S5. Summary of background low-to-moderate TCS use in BREEZE-AD1 and BREEZE-AD2, Week 0 to 16

	BREEZE-AD1				BREEZE-AD2			
	PBO	Bari 1-mg	Bari 2-mg	Bari 4-mg	PBO	Bari 1-mg	Bari 2-mg	Bari 4-mg
	(N=249)	(N=127)	(N=123)	(N=125)	(N=244)	(N=125)	(N=123)	(N=123)
Mean weight (g)	106.1	87.4	48.1	58.4	124.1	101.5	101.4	92.6
SD	176.8	172.1	86.9	123.0	169.4	145.2	159.5	168.8
Reduction in TCS (%)	--	17.6	54.7	44.9	--	18.2	18.3	25.4
P-value vs. PBO	--	0.329	0.001	0.003	--	0.206	0.219	0.094

Bari, baricitinib; g, gram; PBO, placebo; SD, standard deviation; TCS, topical corticosteroids.

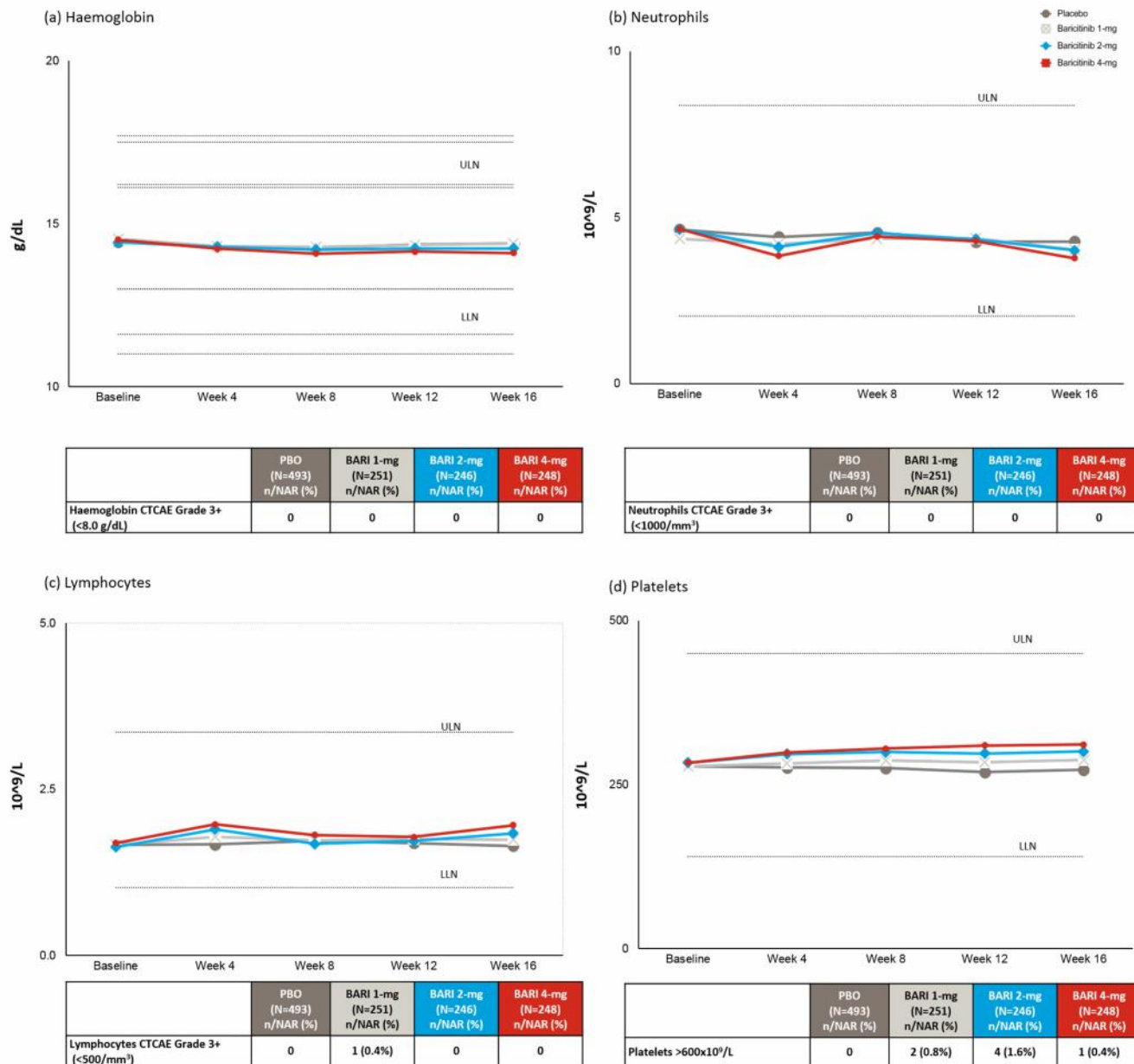
Table S6. Serious adverse events by study

	BREEZE-AD1			
	PBO (N=249)	Bari 1-mg (N=127)	Bari 2-mg (N=123)	Bari 4-mg (N=125)
Dermatitis atopic	2 (0.8)	1 (0.8)	0	1 (0.8)
Alcohol poisoning	0	0	0	1 (0.8)
Breast cancer	1 (0.4)	0	0	0
Clavicle fracture	1 (0.4)	0	0	0
Papillary thyroid cancer	1 (0.4)	0	0	0
Rib fracture	1 (0.4)	0	0	0
Suicide attempt	1 (0.4)	0	0	0
	BREEZE-AD2			
	PBO (N=244)	Bari 1-mg (N=124)	Bari 2-mg (N=123)	Bari 4-mg (N=123)
Tonsillitis	0	0	0	1 (0.8)
Angioedema	0	1 (0.8)	0	0
Asthma	0	1 (0.8)	0	0
Cataract	0	1 (0.8)	0	0
Depression	0	0	1 (0.8)	0
Dermatitis atopic	3 (1.2)	1 (0.8)	1 (0.8)	0
Dermatitis exfoliative generalised	1(0.4)	0	0	0
Diverticulum	0	1 (0.8)	0	0
Drug eruption	0	1 (0.8)	0	0
Eczema herpeticum	2 (0.8)	2 (1.6)	0	0
Encephalitis viral	0	1 (0.8)	0	0
Hypertension	1 (0.4)	0	0	0
Intervertebral disc protrusion	1 (0.4)	0	0	0
Lymphadenopathy	0	1 (0.8)	0	0
Panic attack	0	0	1 (0.8)	0
Peritonsillitis	0	1 (0.8)	0	0
Retinal detachment	1 (0.4)	0	0	0

Data reported as n (%)

Serious adverse event cases are not yet unblinded to investigators and treatment groups cannot be reported.

Figure S11. Laboratory changes in (a) Haemoglobin, (b) Neutrophils, (c) Lymphocytes and (d) Platelets from the combined BREEZE-AD1 and BREEZE-AD2 studies



BARI, baricitinib; CTCAE, Common Terminology Criteria for Adverse Events; LLN, lower limit of normal; NAR, number at risk; PBO, placebo; ULN, upper limit of normal.