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ORIGINAL RESEARCH

# Clinical Tailoring of Baricitinib 2 mg in Atopic Dermatitis: Baseline Body Surface Area and Rapid Onset of Action Identifies Response at Week 16

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## ABSTRACT

**Introduction**: Baricitinib, an oral Janus kinase (JAK)1/JAK2 inhibitor, is indicated in the European Union and Japan for treatment of moderate-to-severe atopic dermatitis (AD) in adults

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who are candidates for systemic therapy. In the ongoing, placebo-controlled, phase 3 trial BREEZE-AD5, once-daily oral baricitinib 2-mg monotherapy improved disease in moderate-to-severe AD patients who had an inadequate response or intolerance to topical corticosteroids. This post-hoc analysis aimed to identify responders to baricitinib 2 mg, using a proposed clinical tailoring approach based on baseline body surface area (BSA) affected and early clinical improvement, in BREEZE-AD5.

**Methods**: Classification and regression tree method was used to evaluate baseline predictors for the proportion of patients achieving ≥ 75% improvement in Eczema Area and Severity Index (EASI75) at week 16 among baricitinib 2-mg-treated patients. Two-by-two contingency tables evaluated the association between early response, defined as ≥ 50% improvement in BSA or ≥ 3-point improvement in Itch Numeric Rating Scale from baseline at weeks 4 or 8, and response at week 16 for the proportion of patients achieving EASI75, validated Investigator Global Assessment for AD (vIGA-AD) score of 0 or 1, or ≥ 4-point improvement in Itch (Itch ≥ 4), respectively. Missing data were imputed as non-responder.

**Results**: At week 16, EASI75 and vIGA-AD (0,1) were achieved by 37.5% and 31.7% of baricitinib 2-mg-treated patients with baseline BSA 10–50% compared with 9.5% and 4.8% with BSA > 50%. Early response in skin inflammation or itch at week 4 was associated with corresponding EASI75, vIGA-AD (0,1), and Itch ≥ 4

of 55.4%, 48.2%, and 39.3% at week 16, while early response at week 8 was associated with 66.7%, 56.1%, and 42.1% of patients achieving these endpoints.

*Conclusion*: Baseline BSA of 10–50% and early clinical improvement after 4 or 8 weeks of baricitinib 2-mg treatment may identify patients most likely to benefit from long-term baricitinib 2-mg therapy.

*Clinical Trial Registration*: NCT03435081.

## PLAIN LANGUAGE SUMMARY

Baricitinib is a medication that helps a dysregulated immune system readjust. This leads to improvements in the inflammatory disease atopic dermatitis (AD). Baricitinib is approved for adults with moderate-to-severe AD in over 40 countries. In the ongoing study BREEZE-AD5, baricitinib 2 mg improved moderate-to-severe AD in patients who previously did not respond to or could not tolerate topical corticosteroids. Understanding which patients are likely to benefit most from a medication can improve patient experience with treatment. It can also ensure that only patients who are likely to benefit from a medication are exposed to it. This analysis aimed to identify patients who are most likely to benefit from baricitinib 2 mg in BREEZE-AD5, using an approach based on baseline body surface area (BSA) affected and early clinical improvement. We showed that patients with moderate-to-severe AD affecting between 10% and 50% of their BSA account for the majority of patients who respond to baricitinib 2 mg after 16 weeks of treatment. Clinical assessment of skin inflammation or itch in patients after 4–8 weeks of initiation of baricitinib 2-mg treatment further improved the ability to identify patients who are most likely to benefit from long-term therapy. This proposed clinical tailoring approach of baseline BSA of 10–50% and early clinical improvement after 4 or 8 weeks of baricitinib 2-mg treatment may allow for the treatment of patients who are most likely to respond to therapy, and rapid decision on discontinuation of treatment for those who are not likely to benefit from baricitinib 2 mg.

**Keywords:** Atopic dermatitis; Baricitinib; Body surface area; Clinical tailoring; Clinical trial; Janus kinase inhibitor

### Key Summary Points

**Why carry out this study?**

Baricitinib, an oral selective Janus kinase (JAK)1/JAK2 inhibitor, is indicated in Europe and Japan for the treatment of moderate-to-severe atopic dermatitis (AD) in adult patients who are candidates for systemic therapy.

Understanding which patients are likely to benefit most from therapy can improve patient experience with treatment, increase the cost-effectiveness of a therapy, and ensure that only patients who are likely to benefit from therapy are exposed to drug.

This post-hoc analysis aimed to identify patients who are likely to benefit from baricitinib 2 mg, using a clinical tailoring approach based on baseline body surface area (BSA) affected and early clinical improvement, in the phase 3 monotherapy trial BREEZE-AD5.

**What was learned from the study?**

Patients with moderate-to-severe AD affecting between 10% and 50% of their BSA account for the majority of week 16 responders to baricitinib 2 mg, and clinical assessment of patients after 4–8 weeks of initiation of baricitinib 2-mg treatment identified those who are likely to benefit from long-term baricitinib 2-mg therapy.

The proposed clinical tailoring approach for baricitinib 2 mg allows for the treatment of patients who are more likely to respond to therapy, and rapid decision on discontinuation of treatment for those who are not likely to benefit from baricitinib 2 mg.

# DIGITAL FEATURES

This article is published with digital features, including a video abstract, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.16989175.

# INTRODUCTION

Atopic dermatitis (AD) is a common, chronic, inflammatory skin disease characterized by complex pathophysiology and heterogeneous clinical phenotypes [1–3]. AD symptoms include intense itch, sleep disturbance, and skin pain, which significantly impact patient quality of life and work productivity [4–6]. Emollients and topical corticosteroids (TCS) are the mainstay of AD therapy [7–9]. In patients with moderate-to-severe AD for whom topical therapy does not adequately control the signs and symptoms of disease, addition of phototherapy and/or systemic treatment is recommended [10, 11]. Systemic treatments can be associated with variable efficacy and unnecessary cycling through ineffective medications resulting in prolonged burden and delayed improvements [10, 12]. Therefore, prediction of treatment efficacy is becoming increasingly important with the emergence of new therapies. An understanding of which patients are most likely to benefit from therapy can help tailor therapies to individual patient needs. Tailored therapeutic approaches can significantly refine the management of AD through improving patient experience with a treatment, increasing cost-effectiveness of a therapy, and ensuring that only patients who are likely to benefit from therapy are exposed to a given treatment.

Baricitinib, an oral selective Janus kinase (JAK) 1 and JAK2 inhibitor [13], is indicated in the European Union and Japan and being evaluated in the USA and other countries for treatment of moderate-to-severe AD in adult patients who are candidates for systemic therapy. Dependent upon country-specific approvals, the recommended starting dose of baricitinib for adults with moderate-to-severe AD is 2 mg or 4 mg [14–16]. In BREEZE-AD5, an ongoing, randomized, placebo-controlled, phase 3 trial of moderate-to-severe AD patients who had an inadequate response or intolerance to TCS, once-daily oral baricitinib 2-mg monotherapy improved several clinical signs and symptoms of AD at week 16 compared with placebo, with a safety profile consistent with previous studies of baricitinib 2 mg in AD [17, 18]. The objective of this post-hoc analysis was to identify patients who are most likely to benefit from baricitinib 2 mg, using a proposed clinical tailoring approach based on baseline body surface area (BSA) affected at drug initiation and early clinical improvement, in the phase 3 monotherapy trial BREEZE-AD5.

# METHODS

## Study Design and Patients

BREEZE-AD5 (NCT03435081) is an ongoing phase 3 randomized, double-blind, placebo-controlled trial conducted in the USA and Canada [17]. Patients ($N = 440$) were randomized 1:1:1 to receive once-daily placebo, baricitinib 1 mg, or baricitinib 2 mg (Fig. S1). Eligible patients were $\geq$ 18 years of age and had a diagnosis of AD, as defined by the American Academy of Dermatology [19], $\geq$ 12 months prior to screening. Enrolled patients had moderate-to-severe disease, defined by baseline Eczema Area and Severity Index (EASI) score $\geq$ 16, validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD) score $\geq$ 3, and BSA involvement of $\geq$ 10%. Patients had a documented history of inadequate response or intolerance to topical therapies within 6 months before screening. Patients discontinued topical therapy 2 weeks and systemic therapy 4 weeks before randomization. This trial was conducted in accordance with the ethical principles of the Helsinki Declaration of 1964 and its later amendments and Good Clinical Practice guidelines and approved by the appropriate institutional review boards/ethics committees at each study site (Table S1), including the Quorum Review IRB (approval #33039). All patients provided written informed consent.

## Outcomes

The primary endpoint of the trial was the proportion of patients who achieved 75% improvement in EASI score (EASI75) at week 16. Two secondary endpoints included the proportion of patients who achieved a vIGA-AD score of 0 (clear) or 1 (almost clear), with a ≥ 2-point improvement from baseline, and the proportion of patients who achieved a ≥ 4-point improvement from baseline in the Itch Numeric Rating Scale (NRS) [17]. These endpoints were analyzed in this post-hoc analysis in the subgroup of patients most likely to benefit from baricitinib 2-mg treatment.

## Statistical Analyses

In this post-hoc analysis, classification and regression tree algorithm (CART) was used to identify baseline predictors of response. A variety of baseline measures were assessed, including, but not limited to patient demographics, prior treatment history, baseline disease severity [such as vIGA-AD, EASI, BSA, Itch NRS, Atopic Dermatitis Sleep Scale, Dermatology Life Quality Index (DLQI), SCORing Atopic Dermatitis, Hospital Anxiety Depression Scale], and laboratory parameters. Response was defined as the proportion of patients achieving EASI75 at week 16 among those treated with baricitinib 2 mg in the intent-to-treat (ITT) population. Two-by-two contingency tables with associated sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were generated between CART-identified baseline predictors and EASI75. As a sensitivity analysis, the same method was applied to identify baseline predictors for the proportion of patients who achieved vIGA-AD (0,1) at week 16. Sensitivity and NPV were examined closely. Sensitivity represents the proportion of patients with certain baseline characteristics, among those who were responders at week 16. A high sensitivity value indicates that most responders were identified by characteristics through the algorithm. NPV represents the proportion of patients who were not responders at week 16, among those without the same baseline

characteristics. A high NPV indicates that patients in this group would likely not benefit from therapy. After baseline subgroups were identified using the CART method, response rate for EASI75, vIGA-AD (0,1), and ≥ 4-point improvement in Itch NRS by visits were analyzed with logistics regression models. Baseline disease severity (vIGA-AD), continuous version of endpoint at baseline, treatment group, baseline subgroup, and treatment-by-baseline subgroup interaction were included as model terms.

After identification of a baseline predictor of response, further analyses were conducted to determine if early response could be used to further refine the patient selection. The goal of this second analysis was to quickly identify any additional patients who are less likely to benefit from therapy and allow for quick clinical decision on whether to transition such patients to alternative therapies. Two-by-two contingency tables were used to evaluate the association between early response in skin inflammation (≥ 50% improvement in BSA) or itch (≥ 3-point improvement in Itch NRS) at week 4 or week 8, and response at week 16 for EASI75, vIGA-AD (0,1), and ≥ 4-point improvement in Itch NRS. Early measures of improvement (≥ 50% improvement in BSA and ≥ 3-point improvement in Itch NRS) were selected for being considered a meaningful improvement, easily noticeable by patients and physicians, and applicable in clinical practice [20]. EASI75, vIGA-AD (0,1), and ≥ 4-point improvement in Itch NRS are accepted regulatory endpoints in AD, which allowed for comparison between the ITT population results and this subgroup analysis. Sensitivity, specificity, PPV, and NPV were used to evaluate the performance of the two-by-two classification table.

Data collected after any rescue or treatment discontinuation were considered as missing. All missing data were imputed as non-responder. To use the same ITT population for evaluating skin inflammation and itch simultaneously in association with early improvement and week 16 response, a conservative approach to define improver and responder was used: any patient with a baseline Itch NRS score < 3 was automatically classified as a non-improver for ≥ 3-

**Table 1** Baseline demographics and disease severity by baseline BSA category

| | BSA 10–50% | | ITT population | | BSA > 50% | |
|---|---|---|---|---|---|---|
| | Placebo (N = 101) | Baricitinib 2 mg (N = 104) | Placebo (N = 147) | Baricitinib 2 mg (N = 146) | Placebo (N = 46) | Baricitinib 2 mg (N = 42) |
| Age (years) | 40.2 (17.2) | 41.2 (14.9) | 39.0 (16.5) | 39.7 (15.0) | 36.4 (14.6) | 36.0 (14.8) |
| Female, n (%) | 47 (46.5) | 65 (62.5) | 67 (45.6) | 77 (52.7) | 20 (43.5) | 12 (28.6) |
| Race, n (%) | | | | | | |
| White | 58 (57.4) | 59 (56.7) | 80 (54.8) | 85 (58.2) | 22 (47.8) | 26 (61.9) |
| African American | 17 (16.8) | 20 (19.2) | 24 (16.4) | 30 (20.5) | 7 (15.2) | 10 (23.8) |
| Asian | 20 (19.8) | 17 (16.3) | 33 (22.6) | 22 (15.1) | 13 (28.3) | 5 (11.9) |
| Other | 6 (5.9) | 8 (7.7) | 9 (6.2) | 9 (6.2) | 3 (6.5) | 1 (2.4) |
| Duration since AD diagnosis (years) | 20.2 (16.4) | 23.9 (16.1) | 22.8 (16.8) | 23.9 (15.9) | 28.6 (16.6) | 24.0 (15.6) |
| vIGA-AD score of 4[a], n (%) | 30 (29.7) | 30 (28.8) | 61 (41.5) | 61 (41.8) | 31 (67.4) | 31 (73.8) |
| EASI[b] | 21.5 (5.7) | 20.9 (4.7) | 27.0 (10.8) | 26.6 (11.4) | 39.0 (9.6) | 40.8 (10.6) |
| Body surface area affected by AD | 27.9 (10.9) | 27.7 (10.7) | 41.5 (23.1) | 39.7 (22.0) | 71.5 (11.6) | 69.5 (12.5) |
| Itch NRS[c] | 6.7 (2.5) | 7.1 (2.3) | 7.0 (2.4) | 7.3 (2.1) | 7.8 (1.8) | 7.8 (1.6) |
| Skin Pain NRS[d] | 6.3 (2.8) | 5.9 (2.5) | 6.5 (2.7) | 6.7 (2.6) | 7.1 (2.6) | 7.4 (2.2) |
| ADSS Item 2[e] | 1.9 (2.0) | 2.6 (3.3) | 2.0 (1.9) | 2.8 (3.2) | 2.3 (1.7) | 3.2 (2.8) |
| DLQI[f] | 13.4 (7.2) | 14.4 (7.4) | 14.7 (7.1) | 15.0 (7.6) | 17.6 (5.9) | 16.3 (7.8) |
| POEM[g] | 19.2 (6.9) | 21.1 (5.4) | 20.5 (6.5) | 21.7 (5.4) | 23.3 (4.2) | 23.1 (5.1) |

Data are mean (SD) unless otherwise indicated

*AD* atopic dermatitis, *ADSS* Atopic Dermatitis Sleep Scale, *BSA* body surface area, *DLQI* Dermatology Life Quality Index, *EASI* Eczema Area and Severity Index, *ITT* Intent-to-Treat, *N* number of subjects in the analysis population, *n* number of subjects in the specified category, *NRS* Numeric Rating Scale, *POEM* Patient Oriented Eczema Measures, *SD* standard deviation, *vIGA-AD* validated Investigator Global Assessment for Atopic Dermatitis

[a]vIGA-AD measures the investigator global assessment of disease severity based on a static 5-point scale from 0 (clear skin) to 4 (severe disease)

[b]EASI scores range from 0 to 72, with higher scores indicating greater severity

[c]Itch NRS ranges from 0 (no itch) to 10 (worst itch imaginable)

[d]Skin Pain NRS ranges from 0 (no pain) to 10 (worst pain imaginable)

[e]ADSS Item 2 assesses the frequency of nighttime awakenings due to itch the previous night on a scale of 0–29

[f]DLQI evaluates health-related quality of life on a scale of 0–30

[g]POEM is a composite measure of patient-reported symptoms, including the effect of symptoms on sleep, and evaluates the frequency of symptoms (including itch) and the effect of atopic dermatitis on sleep on a scale of 0–28

point improvement in Itch NRS at week 4 or 8, and any patient with a baseline Itch NRS score < 4 was automatically classified as a non-responder for ≥ 4-point improvement in Itch NRS at week 16.

# RESULTS

## Classification and Regression Tree Analysis

Baseline BSA was identified as the strongest predictor of treatment outcome to optimize accuracy, with a cutoff of 50% being optimal for sensitivity and NPV. Application of baseline BSA 10–50% to predict response to baricitinib 2 mg resulted in selection of 90.7% (NPV 90.5%) and 94.3% (NPV 95.2%) of EASI75 and vIGA-AD (0,1) responders at week 16, respectively, in the overall study population.
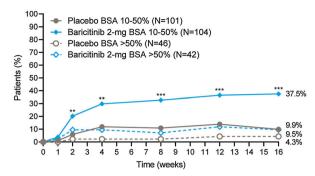
## Baseline Demographics and Disease Severity

Baseline demographics were balanced among the overall ITT population and baseline BSA 10–50% and BSA > 50% subgroups across treatment arms. EASI scores were lower in the BSA 10–50% subgroup compared with the ITT population; however, the overall burden of disease symptoms, including itch, sleep, skin pain, and impact on quality of life, was comparable between the two groups (Table 1).

## Clinical Response among Patients with Baseline BSA 10–50%

We evaluated the impact of baseline BSA on clinical responses to baricitinib 2-mg monotherapy in the ITT population over time. Baricitinib 2 mg resulted in a significantly higher proportion of patients achieving EASI75 and vIGA-AD (0,1) at week 16 in those with baseline BSA 10–50%, but not in BSA > 50% (Fig. 1A and B). Among patients with baseline BSA 10–50%, EASI75 and vIGA-AD (0,1) were achieved at week 16 in 37.5% and 31.7% with baricitinib 2 mg, compared with 9.9% and 6.9% with placebo ($p \leq 0.001$ for both). In contrast, in patients with baseline BSA > 50%, EASI75 and IGA (0,1) responses at week 16 were only achieved in 9.5% and 4.8% with baricitinib 2 mg, compared with 4.3% and 2.2% with placebo ($p$ = not significant for both) (Fig. 1A and B). Response rates for itch were also slightly



**Fig. 1** Clinical response by baseline BSA category. Proportion of patients achieving **A** a 75% improvement in total EASI score, **B** a vIGA-AD score of 0 or 1, or **C** a ≥ 4-point improvement in the Itch NRS response over time, among patients who had a baseline BSA of 10–50% or > 50%. [a]Assessed for patients with a baseline Itch NRS score ≥ 4. *$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$ for baricitinib 2 mg compared with placebo. *BSA* body surface area, *EASI75* 75% improvement in Eczema Area and Severity Index score, *NRS* Numeric Rating Scale, *vIGA-AD (0,1)* validated Investigator Global Assessment for Atopic Dermatitis score of 0 or 1

higher in patients with baseline BSA 10–50% treated with baricitinib 2 mg (Fig. 1C).

Early meaningful response in skin inflammation ($\geq$ 50% improvement in BSA) or itch ($\geq$ 3-point improvement in Itch NRS) at week 8
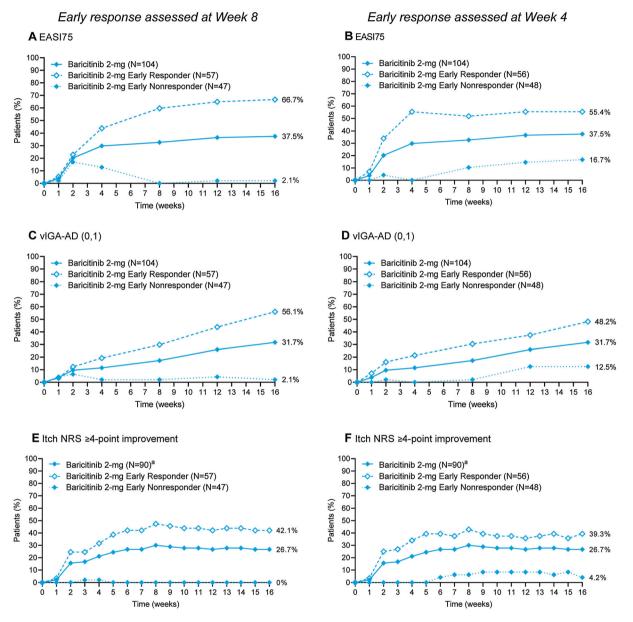


**Fig. 2** Clinical response over time by early response in skin inflammation or itch at week 4 or week 8 among patients with baseline BSA 10–50%. Proportion of patients achieving (**A**, **B**) a 75% improvement in total EASI score, (**C**, **D**) a vIGA-AD score of 0 or 1, or (**E**, **F**) a $\geq$ 4-point improvement in the Itch NRS response over time, among patients with a baseline BSA of 10–50% by early response at week 8 (**A**, **C**, **E**) or week 4 (**B**, **D**, **F**).

Early response in skin inflammation or itch was defined as $\geq$ 50% improvement in BSA or $\geq$ 3-point improvement in Itch NRS, respectively. [a]Assessed for patients with a baseline Itch NRS score $\geq$ 4. *BSA* body surface area, *EASI75* 75% improvement in Eczema Area and Severity Index score, *NRS* Numeric Rating Scale, *vIGA-AD (0,1)* validated Investigator Global Assessment for Atopic Dermatitis score of 0 or 1

or week 4, was able to further refine which patients were most likely to benefit from baricitinib 2-mg therapy longer term (Fig. 2). Among baricitinib 2-mg-treated patients with baseline BSA 10–50%, early response in skin inflammation or itch at week 8 was associated with EASI75, vIGA-AD (0,1), and ≥ 4-point improvement in Itch NRS of 66.7%, 56.1%, and 42.1% at week 16, compared with 2.1%, 2.1%, and 0% for those who did not have an early response at week 8 (Fig. 2A, C, and E). Assessment of early response in skin inflammation or itch at week 4 was associated with corresponding EASI75, vIGA-AD (0,1), and ≥ 4-point improvement in Itch NRS of 55.4%, 48.2%, and 39.3% at week 16, compared with 16.7%, 12.5%, and 4.2% for those who did not have an early response at week 4 (Fig. 2B, D, and F). High NPVs showed that, without early improvement in skin inflammation or itch, there were almost no EASI75, vIGA-AD (0,1), and ≥ 4-point improvement in Itch NRS responders at week 16 with baricitinib 2-mg treatment (Table 2). Among baricitinib 2-mg-treated patients with baseline BSA 10–50%, early response in skin inflammation or itch was associated with improved clinical response at week 16.

# DISCUSSION

Personalized medicine has long been a goal in clinical practice [21, 22]. Providers seek to identify which patients are most likely to benefit from treatment in order to increase the probability of success with a given therapy and minimize risk of exposure to an ineffective treatment. In this study, we demonstrated that baricitinib 2 mg provides enhanced efficacy in patients with a baseline BSA ranging from 10% to 50%, with higher response rates for EASI75 and vIGA-AD (0,1), compared with patients with a baseline BSA > 50%.

Early assessment of clinical response was defined as an improvement of at least 50% in BSA or an improvement of at least 3 points in Itch NRS from baseline at week 4 or week 8. Early response in skin inflammation or itch resulted in an additional significant increase in patient response at week 16 among baricitinib 2-mg-treated patients with baseline BSA 10–50%, with as many as two-thirds of patients achieving an EASI75 at week 16 and over half of the patients achieving a vIGA-AD (0,1) at week 16. This is in contrast to 37.5% and 31.7% of responders observed for EASI75 and vIGA-AD (0,1), respectively, in the overall baseline BSA

**Table 2** Two-by-two contingency tables for clinical response at week 16 by early response in skin inflammation or itch at week 4 or week 8

| Week 16 endpoint | Early-response assessment week | Sensitivity | Specificity | Positive predictive value | Negative predictive value |
|---|---|---|---|---|---|
| EASI75 | Week 4 | 0.795 | 0.615 | 0.554 | 0.833 |
| | Week 8 | 0.974 | 0.708 | 0.667 | 0.979 |
| vIGA-AD (0,1) | Week 4 | 0.818 | 0.592 | 0.482 | 0.875 |
| | Week 8 | 0.970 | 0.648 | 0.561 | 0.979 |
| Itch NRS ≥ 4-point improvement | Week 4 | 0.917 | 0.575 | 0.393 | 0.958 |
| | Week 8 | 1.000 | 0.588 | 0.421 | 1.000 |

Early response in skin inflammation or itch was defined as ≥ 50% improvement in BSA or ≥ 3-point improvement in Itch NRS, respectively

*BSA* body surface area, *EASI* Eczema Area and Severity Index, *NRS* Numeric Rating Scale, *vIGA-AD (0,1)* validated Investigator Global Assessment for Atopic Dermatitis score of 0 or 1

10–50% group, and 29.5% and 24.0%, respectively, in the ITT population [17]. These high efficacy results were observed while maintaining a very high NPV for the analyses, showing that an early decision for discontinuation of therapy is possible in patients with a BSA of 10–50% at baseline. Patients who respond to baricitinib 2 mg experience clinical benefit early in their course of treatment. Patients who do not respond to baricitinib 2-mg treatment within the first 4–8 weeks are unlikely to respond to treatment in the long term.

Although BSA and associated EASI scores were lower in patients with BSA 10–50% at baseline, overall burden of disease by symptoms was comparable between the groups. Patients' baseline itch, sleep disturbance due to itch, skin pain, Patient Oriented Eczema Measures scores, and quality of life (DLQI) were comparable between the groups, confirming the significant burden of disease in patients with baseline BSA 10–50%. Although the proposed clinical tailoring approach uses baseline BSA, a small increase in itch response was also observed in patients with baseline BSA 10–50% compared with patients with baseline BSA > 50%. Importantly, 100% of the patients who responded to baricitinib 2 mg with a $\geq$ 4-point improvement in Itch NRS at week 16 had achieved a $\geq$ 3-point improvement by week 8 (Table 2, sensitivity = 1.0, NPV = 1.0).

A limitation to this study is that these are post-hoc subgroup analyses as opposed to pre-specified subgroup analyses [23]. The analyses focused on the 2-mg dose of baricitinib, and the lack of data from the 4-mg dose is a further limitation. In addition, patients discontinued topical and systemic treatments 2 and 4 weeks prior to randomization, respectively. The discontinuation of topical and systemic therapies weeks prior to the initiation of the study drug may lead to rescue earlier than if therapies were discontinued closer to the initiation of the clinical trial. In addition, this was a monotherapy trial. Although this study helped to better assess the impact of treatment in AD severity without the potential confounding effect of topical corticosteroids, topical calcineurin inhibitors, or topical phosphodiesterase-4 inhibitors, some of these treatments may be maintained in clinical practice during treatment. Other limitations are the lack of standardization in the assessment of BSA [24], as well as the inconsistent performance of a full-body skin examination in clinical practice. The BSA affords a rapid assessment on physical examination that may help to guide clinical decision-making, particularly with the advent of new therapies in the treatment armamentarium for AD.

In conclusion, patients with moderate-to-severe AD affecting between 10% and 50% of their BSA accounted for the majority of responders to baricitinib 2 mg. The clinical assessment of patients after 4–8 weeks of initiation of baricitinib 2-mg treatment predicted which patients are likely to benefit from long-term therapy. This analysis may allow for a precision-medicine approach to therapy in moderate-to-severe AD.

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# REFERENCES

1. Brunner PM, Guttman-Yassky E, Leung DY. The immunology of atopic dermatitis and its reversibility with broad-spectrum and targeted therapies. J Allergy Clin Immunol. 2017;139(4s): S65-s76.

2. Boguniewicz M, Fonacier L, Guttman-Yassky E, Ong PY, Silverberg J, Farrar JR. Atopic dermatitis yardstick: practical recommendations for an evolving therapeutic landscape. Ann Allergy Asthma Immunol. 2018;120(1):10-22.e2.

3. Czarnowicki T, He H, Krueger JG, Guttman-Yassky E. Atopic dermatitis endotypes and implications for targeted therapeutics. J Allergy Clin Immunol. 2019;143(1):1–11.

4. Silverberg JI, Gelfand JM, Margolis DJ, Boguniewicz M, Fonacier L, Grayson MH, et al. Patient burden and quality of life in atopic dermatitis in US adults: a population-based cross-sectional study. Ann Allergy Asthma Immunol. 2018;121(3):340–7.

5. Vakharia PP, Chopra R, Sacotte R, Patel KR, Singam V, Patel N, et al. Burden of skin pain in atopic dermatitis. Ann Allergy Asthma Immunol. 2017;119(6):548-52.e3.

6. Andersen L, Nyeland ME, Nyberg F. Increasing severity of atopic dermatitis is associated with a negative impact on work productivity among adults with atopic dermatitis in France, Germany, the U.K. and the U.S.A. Br J Dermatol. 2020;182(4):1007–16.

7. Eichenfield LF, Tom WL, Berger TG, Krol A, Paller AS, Schwarzenberger K, et al. Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies. J Am Acad Dermatol. 2014;71(1):116–32.

8. Ring J, Alomar A, Bieber T, Deleuran M, Fink-Wagner A, Gelmetti C, et al. Guidelines for treatment of atopic eczema (atopic dermatitis) part I. J Eur Acad Dermatol Venereol. 2012;26(8):1045–60.

9. Katayama I, Aihara M, Ohya Y, Saeki H, Shimojo N, Shoji S, et al. Japanese guidelines for atopic dermatitis 2017. Allergol Int. 2017;66(2):230–47.

10. Sidbury R, Davis DM, Cohen DE, Cordoro KM, Berger TG, Bergman JN, et al. Guidelines of care for the management of atopic dermatitis: section 3. Management and treatment with phototherapy and systemic agents. J Am Acad Dermatol. 2014;71(2):327–49.

11. Ring J, Alomar A, Bieber T, Deleuran M, Fink-Wagner A, Gelmetti C, et al. Guidelines for treatment of atopic eczema (atopic dermatitis) Part II. J Eur Acad Dermatol Venereol. 2012;26(9):1176–93.

12. Renert-Yuval Y, Guttman-Yassky E. New treatments for atopic dermatitis targeting beyond IL-4/IL-13 cytokines. Ann Allergy Asthma Immunol. 2020;124(1):28–35.

13. Fridman JS, Scherle PA, Collins R, Burn TC, Li Y, Li J, et al. Selective inhibition of JAK1 and JAK2 is efficacious in rodent models of arthritis: preclinical characterization of INCB028050. J Immunol. 2010;184(9):5298–307.

14. Olumiant. Australian Product Information. Eli Lilly Australia Pty Ltd. OLUMIANT vA6 Feb_2021. ARTG ID 277905. 2021. https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2018-PI-01225-1. Accessed 25 Mar 2021.

15. Olumiant. European Union Summary of Product Characteristics. Eli Lilly and Company. 2021. https://www.ema.europa.eu/en/documents/product-information/olumiant-epar-product-information_en.pdf. Accessed 23 Mar 2021.

16. Olumiant. Japan Product Information. Eli Lilly and Company. 2021. https://www.info.pmda.go.jp/go/pdf/530471_3999043F1020_1_08. Accessed 21 Sept 2021.

17. Simpson EL, Forman S, Silverberg JI, Zirwas M, Maverakis E, Han G, et al. Baricitinib in patients with moderate-to-severe atopicdermatitis: results from a randomized monotherapy phase 3 trial in the United States and Canada (BREEZE-AD5). J Am Acad Dermatol. 2021;85(1):62–70.

18. King B, Maari C, Lain E, Silverberg JI, Issa M, Holzwarth K, et al. Extended safety analysis of baricitinib 2 mg in adult patients with atopic dermatitis: an integrated analysis from eight randomized clinical trials. Am J Clin Dermatol. 2021;22(3):395–405.

19. Eichenfield LF, Tom WL, Chamlin SL, Feldman SR, Hanifin JM, Simpson EL, et al. Guidelines of care for the management of atopic dermatitis: section 1.

Diagnosis and assessment of atopic dermatitis. J Am Acad Dermatol. 2014;70(2):338–51.

20. Yosipovitch G, Reaney M, Mastey V, Eckert L, Abbé A, Nelson L, et al. Peak Pruritus Numerical Rating Scale: psychometric validation and responder definition for assessing itch in moderate-to-severe atopic dermatitis. Br J Dermatol. 2019;181(4):761–9.

21. Bieber T, D'Erme AM, Akdis CA, Traidl-Hoffmann C, Lauener R, Schappi G, et al. Clinical phenotypes and endophenotypes of atopic dermatitis: where are we, and where should we go? J Allergy Clin Immunol. 2017;139(4s):S58-s64.

22. Renert-Yuval Y, Thyssen JP, Bissonnette R, Bieber T, Kabashima K, Hijnen D, et al. Biomarkers in atopic dermatitis-a review on behalf of the International Eczema Council. J Allergy Clin Immunol. 2021;147(4):1174-90.e1.

23. Curran-Everett D, Milgrom H. Post-hoc data analysis: benefits and limitations. Curr Opin Allergy Clin Immunol. 2013;13(3):223–4.

24. Chopra R, Silverberg JI. Assessing the severity of atopic dermatitis in clinical trials and practice. Clin Dermatol. 2018;36(5):606–15.