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ORIGINAL ARTICLE

Baricitinib treatment rapidly improves the four signs of atopic dermatitis assessed by Eczema Area and Severity Index (EASI) clinical subscores

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Abstract

Background: Baricitinib treatment in adults with moderate-to-severe atopic dermatitis (AD) has demonstrated rapid improvements in itch as well as AD sign severity and affected body surface area as assessed by the Eczema Area and Severity Index (EASI) total score, whether administered as monotherapy or in combination with topical corticosteroids (TCS). As EASI clinical signs differ in time course and associated antecedents, the effects of baricitinib on each individual clinical sign are of interest.

Objectives: In this post hoc analysis, we aimed to investigate the effects of baricitinib on individual EASI subscores, namely excoriation, oedema/papulation, erythema and lichenification, in both monotherapy and TCS combination therapy trials.

Methods: We analysed the percent change from baseline in individual EASI subscores from three phase-III, double-blind, 16-week trials of baricitinib in monotherapy (BREEZE-AD1/BREEZE-AD2) and TCS combination therapy (BREEZE-AD7) cohorts via mixed model repeated measures (MMRM).

Results: Baricitinib 4 mg showed rapid and sustained improvements in all four clinical signs in both cohorts. Significant effects emerged at week 1 for excoriation, oedema/papulation and erythema scores in monotherapy ($p < 0.001$) and TCS combination therapy ($p < 0.001$, $p < 0.01$, $p < 0.001$), plateaued at week 4, and remained significant versus placebo through week 16. The effect on lichenification scores also emerged early, at week 1 in monotherapy ($p < 0.05$) and week 2 in combination therapy ($p < 0.001$), with scores continuously improving without a clear plateau. Effect magnitude was highest in excoriation scores, exhibiting near-maximal reduction in week 1 of monotherapy and remaining highest across all timepoints in combination therapy.

Conclusions: Rapid and sustained improvements were observed across clinical signs of inflammation and particularly on excoriation following baricitinib treatment. Our findings suggest that selective inhibition of janus kinases 1 and 2 leads to rapid and sustained control of skin inflammation, and that rapid reductions in itch translate into early disruption of the itch-scratch cycle.

Andreas Wollenberg and Dagmar Simon contributed equally to this work.

INTRODUCTION

Atopic dermatitis (AD) is a common, heterogeneous, inflammatory skin disorder characterized by frequent, unpredictable flares of highly pruritic skin lesions.[1,2] The clinical signs and symptoms of AD include erythema, xerosis, oedema/papulation, excoriations, lichenification, pruritus (itch), skin pain (soreness, discomfort) and sleep disturbance, which together manifest into a profound disease burden.[3,4]

AD is driven by a complex interplay between inflammation and epidermal dysfunction.[2,3] Acute AD lesions typically display erythema and oedema/papules resulting from heightened inflammation, as well as excoriation marks due to scratching in response to pruritus (see Table 1).[5] This stage is associated with upregulation of mainly T-helper(T_H)2 cytokines.[6–9] Continued damage to the skin barrier via scratching further promotes inflammation, eventually leading to the formation of chronic lesions, marked by lichenification (skin thickening).[5,10–12] The chronic stage of AD is associated with intensification of the T_H2 and T_H22 cytokine axes, along with significant increases in T_H1 and T_H17 markers, cumulatively promoting cutaneous remodelling and neuroinflammation.[1,6–9,13–15] This phenomenon where itch promotes scratching, which imparts damage that promotes itch, is known as the *itch-scratch cycle*.[11,12]

Baricitinib is an oral treatment option for adults with moderate to severe AD who are candidates for systemic therapy. As a selective inhibitor of janus kinases (JAK) 1 and 2, baricitinib transiently inhibits intracellular signalling of pro-inflammatory cytokines, including the T_H2 cytokines IL-4, IL-13 and IL-31; the T_H17/T_H22 cytokine IL-22; and the T_H1-derived cytokine IFN-γ.[1] IL-4, IL-13, and especially IL-31, are also pruritogenic cytokines, promoting AD-related itch through direct or indirect activation of sensory neurons.[1] Accordingly, baricitinib is thought to relieve AD signs and symptoms through reduction of T-cell-driven inflammation in both the acute and chronic stages, along with directly impairing itch transduction.[1] Indeed, large-scale, phase-III clinical trials in adults with moderate to severe AD have found rapid improvements in AD signs and symptoms following baricitinib treatment, either as monotherapy (BREEZE-AD1, BREEZE-AD2) or as combination therapy with topical corticosteroids (TCS) (BREEZE-AD7).[16,17] Outcomes included significant reductions in itch as early as day 2 of treatment,[18] as well as improvements in the Eczema Area and Severity Index (EASI) total score.[16,17]

Recommended by the Harmonizing Outcome Measures for Eczema (HOME) initiative along with the SCORing Atopic Dermatitis (SCORAD) index, and considered one of the best-validated outcome measures for AD, EASI assesses the severity of four key clinical signs of AD, namely excoriation, erythema, oedema/papulation and lichenification (Table 1), as well as the categorized extent of BSA affected.[19–21] Although baricitinib has been proven to improve EASI total scores,[22] reflecting both severity and BSA,[16,17] it is not known whether inhibition of inflammatory and itch-mediating cytokines via baricitinib translates into improvements across all four cutaneous signs assessed by EASI. Therefore, in this post hoc analysis, we aim to examine the effect of baricitinib on each individual EASI sign subscore, thereby elucidating the effect of JAK1/2 inhibition on acute and chronic signs of AD linked to inflammation and/or itch-induced scratching.

METHODS

Methodologies for baricitinib monotherapy trials BREEZE-AD1 (NCT03334396) and BREEZE-AD2 (NCT03334422) and the combination therapy trial BREEZE-AD7 (NCT03733301) have previously been published.[16,17] In brief, these were phase III, double-blind, 16-week trials of baricitinib in adults with moderate to severe AD and a documented history of inadequate response to topical therapies. Participants in BREEZE-AD1/2 ($N = 1239$) were randomized to receive either once-daily oral placebo, 1 mg, 2 or 4 mg baricitinib.[16] Those who participated in BREEZE-AD7 ($N = 329$) were randomized for treatment with either once-daily oral placebo, 2 or 4 mg of baricitinib in combination with moderate- and/or low-potency TCS for active lesions.[17]

Among other measures, changes in disease severity were captured using the EASI total score, a clinical tool that combines measures of lesion intensity with the extent of BSA affected.[19] To assess lesion intensity, body regions were examined for the four key clinical signs of AD (excoriation, erythema, oedema/papulation and lichenification) and assigned a severity subscore from 0 (absent) to 3 (severe) for

TABLE 1 Time course, association with itch, and definition of the four clinical signs of AD captured by EASI.

Clinical sign	Time course[32]	Associated with itch[31]	Definition[5]
Excoriation	Acute & chronic AD	Yes	Physical evidence of pruritus from scratching or rubbing, resulting in broken skin surface.
Edema/Papulation	Acute & chronic AD	No	Edema and papulation representing acute spongiosis and inflammation of the skin.
Erythema	Acute & chronic AD	No	Skin redness caused by increased blood flow to superficial capillaries.
Lichenification	Chronic AD	Yes	Leathery thickening of the epidermis with accentuation of skin markings due to prolonged scratching or rubbing.

Abbreviations: AD, atopic dermatitis; EASI, Eczema Area and Severity Index.

each sign.[5] Averaged across body regions, these subscores form the basis of our analysis.

In this post hoc analysis, we investigated the effect of baricitinib treatment on the four EASI sign subscores individually, separately between monotherapy and TCS combination therapy cohorts. Data from the 1-mg group in BREEZE-AD1/2 were included in the statistical analysis, but we only report outcomes of doses approved for clinical treatment (2 and 4 mg).

Demographics and baseline disease characteristics, including baseline EASI subscores, are summarized below using mean (±SD). EASI subscore percent change from baseline (%CFB) data were analysed using mixed model repeated measures (MMRM) including treatment type, region, baseline disease severity (baseline score on Validated Investigator Global Assessment for Atopic Dermatitis, vIGA-AD[16,17]), visit, and treatment-by-visit interaction as fixed effects, and baseline EASI subscore and baseline EASI subscore-by-visit interaction as fixed continuous effects. EASI subscores collected after first rescue therapy date or permanent study drug discontinuation were excluded from the analysis and no multiplicity was adjusted for the comparisons. Patients with a baseline score of 0 for a particular sign were not included in analysis of that sign.

RESULTS

Baseline characteristics

General participant characteristics at baseline have previously been reported.[16,17] In brief, mean (±SD) age of participants receiving monotherapy (BREEZE-AD1/2; $N = 1239$) was 35.2 years (±12.8), with 37.7% of the cohort female and 63.5% White. Meanwhile, those receiving combination therapy (BREEZE-AD7; $N = 329$) were of a mean (±SD) age of 33.8 (±12.4), with 34.3% female and 45.6% White.

Mean (±SD) baseline itch scores on the itch numerical rating scale (itch NRS) were 6.6 (±2.1) in the monotherapy and 7.1 (±2.0) in the combination therapy cohort. Baseline mean (±SD) EASI total scores were 32.2 (±13.0) and 29.6 (±12.3) in the monotherapy and combination therapy cohorts respectively. Such high EASI total scores, indicative of severe disease,[5] reflect the extensive nature of the chronic AD present in this sample population. Baseline EASI subscores were similar across treatment arms within each cohort, with erythema scores generally higher than other signs in both the monotherapy and the combination therapy cohort (see Table 2).

Excoriation: Baricitinib therapy results in rapid and sustained improvement in a sign closely related to itch

Following baricitinib 4 mg monotherapy, excoriation scores significantly differed from placebo starting at week 1 ($p < 0.001$). Relative to placebo, the reduction of excoriations by 17.5% was the highest observed among all subscores (14.6%, 14.4% and 11.8% for oedema/papulation, erythema and lichenification, respectively) at this early timepoint (Figure 1a–d). The magnitude of the effect appeared to plateau at week 4 [mean %CFB 4-mg: −45.1% (±2.7%); placebo: −21.1% (±2.3%)], with improvement maintained thereafter. At week 16, the mean %CFB was −44.1% (±3.4%) for 4 mg, −43.6% (±3.8%) for 2 mg, and −25.0% (±3.2%) for placebo (both doses $p < 0.001$ vs. placebo).

Baricitinib 4 mg + TCS combination therapy also resulted in significant reduction of excoriation scores compared to placebo + TCS, seen from week 1 ($p < 0.001$) through week 16. As in the monotherapy cohort, the effect appeared to plateau at week 4 [4 mg: −63.2% (±3.3%); placebo: −30.3% (±3.4%)]. At week 16, mean %CFB was −56.7% (±4.3%) for 4 mg ($p < 0.01$ vs. placebo), −47.8% (±4.3%) for 2 mg (*n.s.* vs. placebo) and −36.7% (±4.5%) for placebo (Figure 2a). Across all timepoints, the effect size of 4 mg versus placebo remained notably higher in excoriation (mean effect size: 24.8%) than the other subscores (17.7%, 14.7% and 7.9% in oedema/papulation, erythema and lichenification scores respectively) (Figure 2a–d).

TABLE 2 Baseline EASI subscores between cohorts.

	Monotherapy			Combination therapy		
Signs (score range: 0–3)	**PBO ($n = 492$)**	**2 mg ($n = 244$)**	**4 mg ($n = 247$)**	**PBO ($n = 108$)**	**2 mg ($n = 109$)**	**4 mg ($n = 111$)**
Excoriation	1.92 (±0.55)	1.96 (±0.54)	1.91 (±0.58)	1.84 (±0.56)	1.78 (±0.55)	1.83 (±0.57)
Lichenification	2.05 (±0.55)	2.07 (±0.52)	2.02 (±0.54)	1.90 (±0.51)	1.86 (±0.53)	1.89 (±0.53)
Erythema	2.26 (±0.46)	2.25 (±0.48)	2.25 (±0.45)	2.16 (±0.46)	2.11 (±0.39)	2.24 (±0.45)
Edema/Papulation	1.99 (±0.56)	2.00 (±0.58)	1.96 (±0.58)	1.91 (±0.51)	1.83 (±0.57)	1.97 (±0.44)

Note: Baseline EASI subscores of trial participants prior to initiating treatment; those in the monotherapy cohort were randomized to receive either placebo or baricitinib, while those in the combination therapy trial were assigned placebo or baricitinib (oral, once daily) along with ad lib. use of TCS. Data presented as mean (± SD). Four participants receiving monotherapy ($n = 1$ for placebo, $n = 2$ for 2 mg baricitinib, and $n = 1$ for 4 mg baricitinib) and one participant receiving combination therapy ($n = 1$ for placebo + TCS) were excluded from percent change from baseline (%CFB) analysis due to a baseline score of 0 for a clinical sign.

Abbreviations: %CFB, percent change from baseline; EASI, Eczema Area and Severity Index; PBO, placebo; SD, standard deviation; TCS, topical corticosteroids.

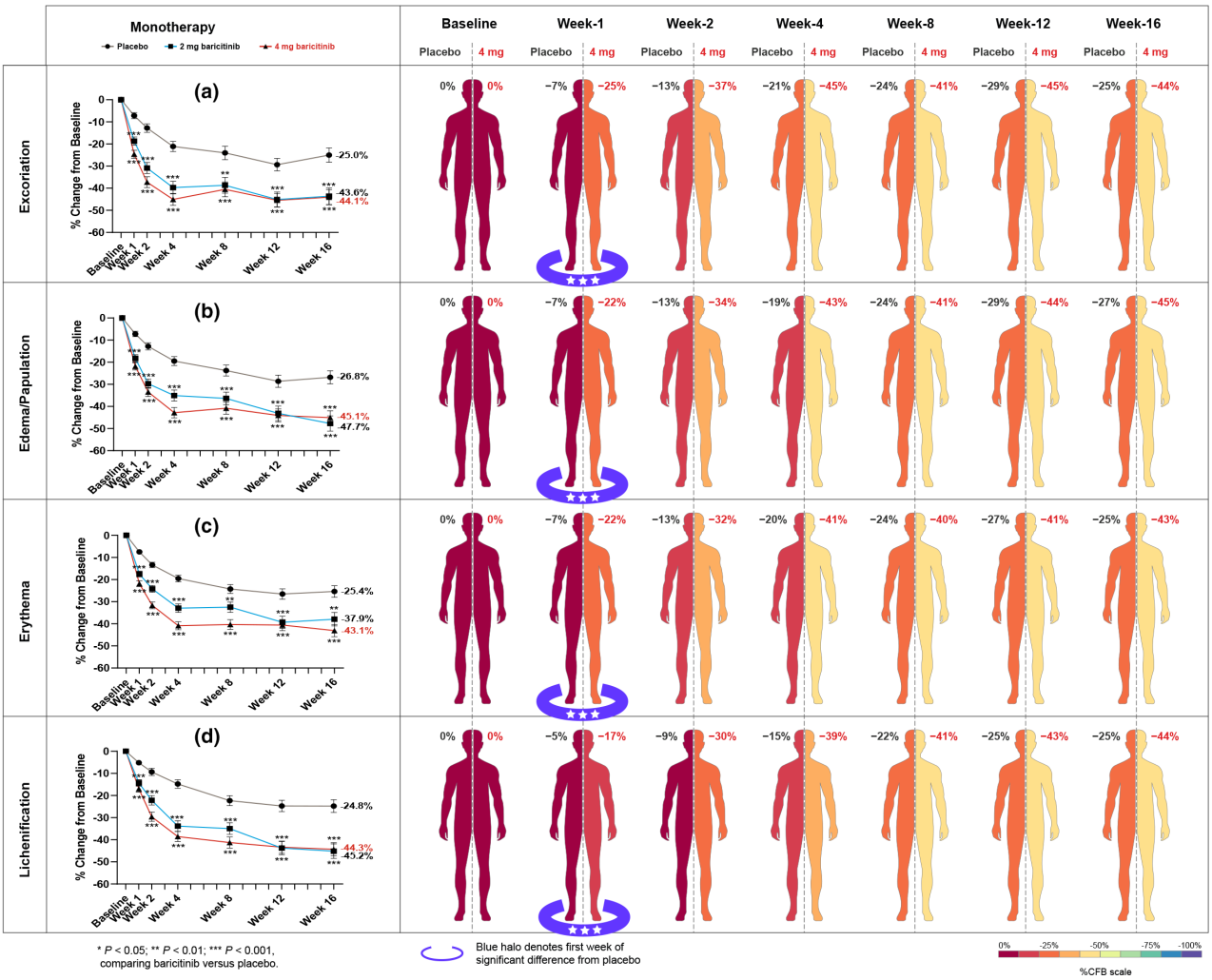

FIGURE 1 Line graphs depict percent change from baseline (%CFB) in the four EASI subscores (panel a, excoriation; panel b, oedema/papulation; panel c, erythema; panel d, lichenification) across 16 weeks of monotherapy with oral placebo, or 2 mg or 4 mg baricitinib. Homunculi depict the difference in %CFB between placebo (lefthand side) and 4 mg baricitinib (righthand side), illustrating effects of baricitinib versus placebo across four signs of moderate-to-severe AD captured by EASI over 16 weeks of treatment. AD, atopic dermatitis; %CFB, percent change from baseline; EASI, eczema area and severity index.

Oedema/Papulation and erythema: Baricitinib shows rapid and sustained improvements in AD signs reflecting skin inflammation

Baricitinib 4 mg monotherapy rapidly improved oedema/papulation scores, differing significantly from placebo from week 1 ($p < 0.001$) through week 16, with the effect largely plateauing at week 4 [4 mg: −42.8% (±2.4%); placebo: −19.5% (±2.0%)]. At week 16, mean %CFB was −45.1% (±3.1%) for 4 mg, −47.7% (±3.5%) for 2 mg and −26.8% (±3.0%) for placebo (both doses $p < 0.001$ vs. placebo) (Figure 1b).

Combination of baricitinib 4 mg with TCS enhanced the reduction in oedema/papulation scores relative to monotherapy, also significantly differing from placebo + TCS from week 1 ($p < 0.01$), with the effect plateauing at week 4 [4 mg: −53.0% (±3.1%); placebo: −26.1% (±3.2%)]. At week 16, mean %CFB was −51.8% (±3.8%) for 4 mg ($p < 0.01$ vs. placebo), −45.8% (±3.8%) for 2 mg (*n.s.* vs. placebo) and −36.5% (±3.9%) for placebo. Notably, at week 16, the effect size for 4 mg versus placebo (15.3%) was smaller than in the monotherapy cohort (18.3%) (Figure 2b).

Akin to oedema/papulation, erythema scores showed rapid and sustained improvement following baricitinib 4 mg monotherapy. Scores were significantly different from placebo at week 1 ($p < 0.001$) and plateaued by week 4 [4 mg: −40.9% (±1.8%); placebo: −19.5% (±1.5%)]. At week 16, mean %CFB was −43.1% (±2.8%) for 4 mg ($p < 0.001$ vs. placebo), −37.9% (±3.1%) for 2 mg ($p < 0.01$ vs. placebo) and −25.4% (±2.6%) for placebo (Figure 1c).

Similarly, baricitinib 4 mg + TCS combination therapy was followed by significant improvements in erythema scores compared to placebo + TCS, starting at week 1 ($p < 0.001$) and lasting through study end, with the effect plateauing at week 4 [4 mg: −47.0% (±2.7%); placebo: −26.8% (±2.7%)]. At week 16, mean %CFB was −47.0% (±3.1%) for 4 mg ($p < 0.01$ vs. placebo), −41.1% (±3.1%) for 2 mg (*n.s.* vs. placebo), and −32.4% (±3.2%) for placebo. As with oedema/papulation scores, the mean effect size of 4 mg vs. placebo

FIGURE 2 Line graphs depict %CFB in the four EASI subscores (panel a, excoriation; panel b, oedema/papulation; panel c, erythema; panel d, lichenification) across 16 weeks of combination therapy with oral placebo, or 2 mg or 4 mg baricitinib, in conjunction with ad lib. use of TCS. Homunculi depict the difference in %CFB between placebo (lefthand side) and 4 mg baricitinib (righthand side), illustrating effects of baricitinib versus placebo across four signs of moderate-to-severe AD captured by EASI over 16 weeks of treatment. AD, atopic dermatitis; %CFB, percent change from baseline; EASI, eczema area and severity index; TCS, topical corticosteroids.

(14.7%) was smaller than observed in monotherapy (17.0%) (Figure 2c).

Lichenification: Baricitinib therapy results in gradual improvement in the clinical sign associated with chronic AD

Lichenification scores improved following baricitinib 4 mg monotherapy, albeit with slower kinetics. Although scores differed significantly from placebo from week 1 ($p < 0.001$), the reduction versus placebo of 11.8% was relatively small compared to all other subscores at this early timepoint. Moreover, lichenification scores exhibited continuous gradual improvement rather than a plateau. At week 16, mean %CFB was −44.3% (±3.0%) for 4 mg, −45.2% (±3.3%) for 2 mg and −24.8% (±2.8%) for placebo (both doses $p < 0.001$ vs. placebo) (Figure 1d). Compared to other subscores at week 16, the 19.5% effect size of 4 mg versus placebo in lichenification reduction appeared notably high (19.1%, 18.3% and 17.7% in excoriation, oedema/papulation and erythema respectively).

Unlike monotherapy, the reduction in lichenification scores was not significantly different between baricitinib 4 mg + TCS and placebo + TCS until week 2 ($p < 0.05$); thereafter, the difference was only significant at weeks 4 and 12. At week 16, mean %CFB was −45.8% (±3.6%) for 4 mg, −42.6% (±3.7%) for 2 mg and −35.7% (±3.8%) for placebo, neither significantly different from placebo. Accordingly, the effect size for 4 mg versus placebo was markedly smaller (mean: 7.9%) than seen in the other subscores. The effect of 2 mg did not significantly differ from placebo at any time point analysed (Figure 2d).

DISCUSSION

Baricitinib treatment consistently improved all clinical signs of AD as assessed by EASI subscores, both in

monotherapy and TCS combination therapy. For excoriation, erythema and oedema/papulation scores, the effect emerged as early as week 1, plateaued at week 4, and was maintained thereafter to study end at week 16, with excoriation scores demonstrating the highest magnitude of reduction. In contrast, especially in the monotherapy cohort, lichenification scores exhibited continuous improvement in response to baricitinib therapy without a clear plateau by study end. This slow response of lichenification scores is probably owing to the fact that lichenification is a sign of chronic lesions and tissue remodelling. While it has previously been shown that patients treated with baricitinib show improvements in EASI total scores, including reductions in the overall affected BSA,[16,17] this post hoc analysis adds detailed information regarding the effects of baricitinib on the individual clinical signs of AD. Our findings indicate that a rapid reduction of itch upon baricitinib therapy as previously reported[18] translates into a rapid and notable improvement of excoriation. Moreover, the observed improvements of erythema and oedema/papulation indicate rapid and sustained control of skin inflammation through selective inhibition of JAK1/2.

Considered the most burdensome AD symptom,[4] itch is reflected clinically by excoriation marks arising from excessive scratching, further perpetuating signs and symptoms via the *itch–scratch cycle*.[11,12] In the current analysis, we observed a particularly beneficial effect of baricitinib on excoriation that emerged at highest magnitude as early as 1 week after treatment initiation and reached a maximal plateau after 4 weeks. The effect of TCS combination therapy was even more pronounced than monotherapy. These findings suggest that the previously reported reductions in itch[16,17]—after only 1 day of baricitinib treatment[18]—has rapid effects on scratching, indicating early disruption of the itch–scratch cycle. The resulting profound and early reduction in excoriation marks might further relate to reports that baricitinib treatment reduces the incidence rate of skin infections requiring antibiotic treatment, as pathogens might be transferred to or into the epidermis via mechanical damage.[23] The direct and rapid effect of baricitinib on itch reduction likely stems from inhibition of key itch mediators including TSLP, IL-4, IL-13 and especially IL-31.[1] Overall, these findings may help physicians make treatment decisions for patients who suffer from intense pruritus and are having difficulty disrupting the itch–scratch cycle. A subset of AD patients of special relevance are known as the 'itch-dominant phenotype', who appear to require greater medical attention.[24] It has recently been demonstrated that these patients, defined as having itch NRS ≥7 and 10%–40% affected BSA, are precisely those who are most likely to benefit from baricitinib.[25]

Rapid and sustained improvements emerging as early as 1 week after treatment initiation and persisting through week 16 were also observed for oedema/papulation and erythema scores following baricitinib treatment, both in mono- and TCS combination therapy. However, the effect size of baricitinib 4 mg versus placebo in these two subscores was noticeably smaller in TCS combination therapy than in monotherapy, reflecting the short-term anti-inflammatory background effects of TCS on these clinical hallmark signs of inflammation.[5] Accordingly, the improvements seen with baricitinib in both mono- and TCS combination therapy point towards rapid reduction in inflammation following JAK1/2 inhibition. Many cytokines involved in the AD inflammatory response signal via JAK1 and/or JAK2, including IL-4, IL-5 and IL-13.[1] Across all four clinical signs, erythema scores were highest at baseline, indicating that these patients had pronounced erythema at baseline (see Table 2). Facial redness is a recognized issue in patients with AD.[26] Previous work has shown that baricitinib therapy leads to rapid and substantial reductions in severity of AD signs in the highly visible head/neck region, including in erythema.[27] Given that the majority of adults with AD report worrying about their appearance[28] and wish 'to get better skin quickly',[29] such rapid improvements in erythema and oedema/papulation are likely of importance to patients.

Chronic inflammation and prolonged scratching impart repeated damage to the skin barrier, leading to acanthosis, tissue remodelling, and eventually lichenification, a typical sign of chronic AD lesions.[1,9,13,14,30,31] In line with the chronic nature, and in contrast to the other clinical signs which reached a maximal plateau after 4 weeks, lichenification scores in both cohorts continued to exhibit gradual improvements through study end, particularly in the monotherapy cohort. A slower response of lichenification scores to baricitinib therapy is expected since the resolution of acanthosis and tissue remodelling is thought to be secondary to the reduction of inflammation and itch.[1] Despite being slower to emerge, the effect size of baricitinib 4 mg versus placebo on lichenification scores was the largest across the four clinical signs after 16 weeks of monotherapy. Beneficial effects over time might be related to the inhibition of cytokines associated with lichenification that signal via JAK1/2, such as T_H17 and T_H1 cytokines, particularly IL-22, IL-23 and IFNγ.[1] In TCS combination therapy, however, lichenification scores showed only marginal differences between baricitinib 4 mg and background TCS (and no statistically significant benefit of baricitinib 2 mg) and did not reach significance until week 2 of treatment. The difference between mono- and TCS combination therapy cohorts in time course and effect size implicates the notable, albeit short-term, background effects of TCS on lichenification. With direct effects on keratinocytes and fibroblasts, it is known that TCS can improve lichenification, though the effect is only transient.[10,17] We have previously shown that baricitinib reduces the need for TCS.[17] These findings, particularly the results from monotherapy trials, indicate a marked effect of baricitinib on lichenification, especially long term, which might be linked to reductions in chronic inflammation and cessation of prolonged scratching due to alleviation of persistent itch.

One of the limitations of this post hoc analysis is that subscores were averaged across body regions, which may have precluded finding region-specific effects. Additionally, this analysis was limited to a 16-week study period. It is possible that this timeframe was too short to capture the full effect

of baricitinib treatment, particularly on signs of chronic AD that may respond more slowly to treatment. However, many of the participants have continued on to BREEZE-AD3 (NCT03334435), an ongoing long-term extension study. As such, it may be possible to conduct further analyses in the future.

In conclusion, this post hoc analysis indicates that inhibition of JAK1/2 via baricitinib leads to rapid and sustained effects across key clinical signs of AD, both in monotherapy and TCS combination therapy, with gradual ongoing improvements in lichenification reflecting chronic AD. These findings, along with the particularly early and profound reductions in excoriation marks, support the direct effects of baricitinib on reducing inflammation and alleviating itch in AD. This is in line with our understanding of the need for disrupting the itch–scratch cycle in order to successfully treat moderate-to-severe AD.

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DATA AVAILABILITY STATEMENT

Lilly provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the US and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.

ETHICS STATEMENT

Protocols for all studies included in this analysis were approved by the Institutional Review Board or Ethics Committee at each participating site. All studies included in this analysis were conducted in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all eligible participants before undergoing study-related procedures.

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