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Early improvements in signs and symptoms predict clinical response to baricitinib in patients with moderate-to-severe atopic dermatitis

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Abstract

Background Early prediction of therapeutic response can optimize treatment strategies in atopic dermatitis (AD). Baricitinib is approved for moderate-to-severe AD in Europe, Japan and other countries.

Objectives To identify early clinical improvements that can reliably predict a later clinical response to baricitinib in adults with moderate-to-severe AD.

Methods Using data from one topical corticosteroid combination study [BREEZE-AD7 (NCT03733301)] and data pooled from two monotherapy studies [(BREEZE-AD1 (NCT03334396) and BREEZE-AD2 (NCT03334422)], we calculated the sensitivity and specificity, along with the positive predictive value (PPV) and negative predictive value (NPV), of predefined changes in single and combined clinical scores at weeks 2, 4 and 8, to predict clinical response at week 16. Clinical response was defined as $\geq$ 75% improvement in Eczema Area and Severity Index (EASI 75), $\geq$ 4-point improvement in Itch Numeric Rating Scale (Itch NRS $\geq$ 4), or a combination of both.

Results Composite predictors had higher predictive accuracy for week 16 response outcomes than did single parameters. This was evident as early as week 4 for the combination of EASI 50 or Itch NRS $\geq$ 3 and of validated Investigator Global Assessment for AD (vIGA-AD) score $\leq$ 2 or Itch NRS $\geq$ 3 (sensitivity 87–100%; NPV 68–100%). The predictive accuracy of these composite clinical predictors for week 16 response outcomes was highest at week 8 (sensitivity 92–100%; NPV 80–100%). At both weeks 4 and 8, EASI 50 or Itch NRS $\geq$ 3 had higher sensitivity and NPV than did vIGA-AD score $\leq$ 2 or Itch NRS $\geq$ 3.

Conclusions Improvement in signs and symptoms early during treatment with baricitinib 4 mg once daily predicts clinical response at week 16, providing a tool for dermatologists when choosing treatment strategies for patients with moderate-to-severe AD.

What is already known about this topic?

- Response-guided therapy, using identified early predictors of response, allows timely identification of patients likely to benefit from a particular treatment and helps physicians to optimize treatment decisions.
- Baricitinib, an oral selective inhibitor of Janus kinases 1 and 2, is approved for the treatment of adults with moderate-to-severe atopic dermatitis (AD), with documented fast onset of efficacy in clinical trials.

What does this study add?

- This study identified a $\geq$ 50% reduction in Eczema Area and Severity Index (EASI 50) score or $\geq$ 3-point improvement in Itch Numeric Rating Scale (NRS $\geq$ 3) and validated Investigator Global Assessment for AD (vIGA-AD) $\leq$ 2 or Itch NRS $\geq$ 3 at week 4 or 8 after treatment initiation as reliable predictors of clinical response to baricitinib, both as monotherapy and in combination with topical corticosteroids, at week 16.
- Early predictor analysis can inform therapeutic decision-making for physicians and optimize the benefit/risk ratio for patients with AD who initiate treatment with baricitinib.

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Baricitinib is an oral selective and reversible inhibitor of Janus kinase family members 1 and 2 (JAK1, JAK2), and is indicated for the treatment of moderate-to-severe atopic dermatitis (AD), with or without topical corticosteroids (TCS), in adult patients who are candidates for systemic therapy in a number of regions including Europe and Japan.[1] It is currently being evaluated for this indication in the USA. In phase III clinical studies, once-daily (OD) oral baricitinib significantly improved skin inflammation and itch compared with placebo in patients with moderate-to-severe AD who had an inadequate response to topical therapies. Significant improvements were observed in some endpoints as early as 1 week after initiation of treatment with baricitinib.[2,3] As with other systemic treatments for AD, not all patients reached the primary study endpoint.

Patients with moderate-to-severe AD often require long-term systemic treatment to achieve and maintain disease control; therefore, consideration of the benefit/risk associated with the use of a therapy is an important aspect of clinical care.[4,5] Clinical outcome parameters that can, at an early timepoint in treatment, reproducibly predict a defined clinical response at later timepoints, can optimize patient management in AD. Such optimization can be achieved by avoiding prolonged exposure to a drug in those patients unlikely to gain a therapeutic benefit and by facilitating timely decision-making for treatment alternatives.[6]

Given the rapidity of improvement in the signs and symptoms of AD that occurs among baricitinib responders,[2,3] the aim of this analysis was to determine if changes in disease severity measures at early timepoints during treatment can predict a clinical response at week 16 in patients receiving baricitinib as monotherapy or in combination with TCS.

Patients and methods

Studies

This analysis used data from all phase III trials with relevant data; these trials were the monotherapy, multicentre, randomized, double-blind studies BREEZE-AD1 (NCT03334396) and BREEZE-AD2 (NCT03334422),[2] and the TCS combination, multicentre, randomized, double-blind, placebo-controlled study BREEZE-AD7 (NCT03733301).[3] We considered studies relevant if they were phase III, included a baricitinib 4 mg treatment group, and were conducted in patients with moderate-to-severe AD who had an inadequate response to topical therapies and evaluated the first 16 weeks of baricitinib, that is, we considered studies that reflect the current baricitinib label and followed patients for the period immediately after baricitinib initiation. The analysis was prespecified for the BREEZE-AD7 study. Full methodological details of these studies have been published previously.[2,3] Briefly, patients with moderate-to-severe AD were randomized to 16 weeks of OD treatment with baricitinib 1 mg, 2 mg or 4 mg or placebo in BREEZE-AD1 and BREEEZE-AD2, and baricitinib 2 mg or 4 mg or placebo, in combination with TCS, in BREEZE-AD7. Two groups of patients were considered in this analysis: data from patients randomized to baricitinib 4 mg OD (intention-to-treat) in BREEZE-AD1 and BREEZE-AD2 were pooled; and data from patients randomized to baricitinib 4 mg OD plus TCS (intention-to-treat) from BREEZE-AD7 were analysed separately.

This analysis was restricted to data for baricitinib 4 mg OD, as this dose achieved statistical significance in the multiplicity analysis for the assessed efficacy outcomes at week 16 across all clinical trials. Patient data obtained after discontinuation of study treatment or initiation of rescue therapy (with TCS or other systemic therapy) were censored as missing and underwent nonresponder imputation.

The primary endpoint of the BREEZE-AD1, BREEZE-AD2 and BREEZE-AD7 studies was the percentage of participants achieving a validated Investigator Global Assessment for AD of 0 or 1 (vIGA-AD 0,1) with a $\geq$2 point improvement at week 16.[2,3] Key secondary endpoints included the proportion of patients achieving $\geq$ 75% improvement in Eczema Area and Severity Index (EASI 75) at week 16 and the proportion of patients with $\geq$4-point improvement in Itch Numeric Rating Scale (Itch NRS $\geq$ 4) among patients with baseline score $\geq$4 at weeks 1, 2, 4 and 16.

All three clinical trials were conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines, and were approved by institutional review boards or ethics committees at each study site. All patients provided written informed consent before any study-related procedures were undertaken.

Response outcomes

To determine response outcomes at week 16, the proportions of patients with EASI 75, Itch NRS $\geq$ 4 or the composite response outcome of EASI 75 or Itch NRS $\geq$ 4 were assessed.

Clinical response predictors

The following parameters that encompassed clinician-assessed and patient-reported improvements in disease severity were tested as potential clinical predictors of response to baricitinib: EASI 50, vIGA-AD $\leq$ 2 and Itch NRS $\geq$ 3. Improvements were evaluated at weeks 2, 4 and 8 after treatment initiation. The three parameters were assessed individually and as composite predictors by combining EASI 50 or Itch NRS $\geq$ 3 and vIGA-AD $\leq$ 2 or Itch NRS $\geq$ 3, resulting in a total of five potential clinical response predictors, three of which denote an intermediate response in relation to the respective efficacy outcomes (i.e. EASI 50 vs. EASI 75, Itch NRS $\geq$ 3 vs. Itch NRS $\geq$ 4, and the respective combinations). The composite endpoints were selected to include both early objective skin improvement and early key symptom improvement.

Statistical analyses

Two-by-two contingency tables were generated to examine relationships between potential clinical predictors and response outcomes. Sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) for each combination of response outcome and potential clinical predictor were assessed to evaluate the accuracy of each individual clinical predictor at weeks 2, 4 and 8. Analyses were conducted using R version 3.6.0.[7]

Table 1 Baseline characteristics of patients with moderate-to-severe atopic dermatitis (AD) treated with baricitinib 4 mg once-daily (OD) monotherapy in the BREEZE-AD1 and BREEZE-AD2 studies and in combination with topical corticosteroids in the BREEZE-AD7 study

	Pooled BREEZE-AD1 and BREEZE-AD2 baricitinib 4 mg OD subgroups (*N* = 248)	BREEZE-AD7 baricitinib 4 mg OD subgroup (*N* = 111)
Age (years)	35.5 (13.6)	34 (11.4)
Female, *n* (%)	83 (33.5)	36 (32.4)
Weight (kg)	73.5 (16.1)	73.3 (17.8)
BMI (kg m^{-2})	25.1 (4.3)	25.1 (5.1)
Geographical region, *n* (%)		
Europe	132 (53.2)	39 (35.1)
Japan	45 (18.1)	22 (19.8)
Other[a]	71 (28.6)	50 (45.0)
Population, *n* (%)		
White	152 (61.3)	54 (48.6)
Asian	79 (31.8)	54 (48.6)
Time since AD diagnosis (years)	23.7 (14.9)	25.5 (13.2)
vIGA-AD[b] score of 4, *n* (%)	114 (46.0)	50 (45.0)
EASI[c]	32.5 (12.7)	30.9 (12.6)
SCORAD[d]	67.9 (13.2)	68.3 (13.2)
Percentage BSA affected	52.9 (21.6)	52.1 (23.3)
Itch NRS[e]	6.5 (2.1)	7.0 (0.2)
DLQI[f]	13.7 (7.7)	14.7 (7.9)
Asthma, *n* (%)	74 (29.8)	32 (28.8)
Allergic rhinitis, *n* (%)	86 (34.7)	45 (40.5)

Data are presented as mean (SD) unless otherwise stated. BMI, body mass index; BSA, body surface area; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; NRS, Numeric Rating Scale; SCORAD, SCORing Atopic Dermatitis; vIGA-AD, validated Investigator Global Assessment for Atopic Dermatitis. [a]'Other' represents India, Mexico and Taiwan for BREEZE-AD1; Argentina, Australia, Israel and South Korea for BREEZE-AD2; and Argentina, Australia, South Korea and Taiwan for BREEZE-AD7. [b]vIGA-AD measures the IGA of disease severity based on a static 5-point scale from 0 (clear skin) to 4 (severe disease). [c]EASI scores range from 0 to 72, with higher scores indicating greater severity. [d]SCORAD is a combined score of investigator-reported disease severity and affected BSA, and patient-reported symptoms of itch and sleep dysfunction; scores range from 0 to 103. [e]Itch NRS, ranging from 0 (no itch) to 10 (worst itch imaginable). [f]DLQI evaluates health-related quality of life on a scale of 0–30.

Sensitivity, in this context, was defined as the proportion of patients with an early response among those patients with a response at week 16 (i.e. patients with an early response and a response at week 16/all patients with a response at week 16). Specificity was defined as the proportion of patients without an early response among those patients who had no response at week 16 (i.e. patients without an early response and with no response at week 16/all patients with no response at week 16). PPV was defined as the proportion of patients with an early response and a response at week 16 among those with an early response (i.e. patients with an early response and a response at week 16/all patients with an early response irrespective of response at week 16). Conversely, NPV was defined as the proportion of patients without an early response who continued to have no response at week 16 among patients without an early response (i.e. patients without an early response who continued to have no response at week 16/all patients without an early response irrespective of response at week 16).

High values for sensitivity and NPV were therefore considered most relevant when assessing predictors to ensure accurate identification of patients who would benefit from continued treatment while minimizing treatment exposure in those who were unlikely to benefit.

Graphical representations of responder rates over time by early responder vs. nonresponder, as defined by each outcome, were generated for timepoints that looked promising, and were used to confirm the strongest clinical predictors.

Results

Baseline characteristics of patients included in this analysis, all of whom were treated with baricitinib 4 mg OD, were similar to those of the respective placebo and other baricitinib dose groups in each study.[2,3] AD severity was similar between the pooled monotherapy (BREEZE-AD1 and BREEZE-AD2) and TCS combination therapy (BREEZE-AD7) groups, with mean EASI and SCORing Atopic Dermatitis (SCORAD) scores indicating severe disease and a mean (SD) body surface area (BSA) affected of 52.9% (21.6) and 52.1% (23.3) in the two cohorts, respectively (Table 1).

Individual measures of early disease improvement as predictors of response to baricitinib 4 mg showed predictive value at weeks 4 and 8 for all three outcomes at week 16 (Tables 2–4). However, composite predictors that captured both improvement of skin signs and itch had consistently higher sensitivity and NPVs than single parameters. This was evident as early as week 4 for the combination of EASI 50 or Itch NRS $\geq$ 3 and vIGA-AD $\leq$ 2 or Itch NRS $\geq$ 3 (sensitivity 87–97%; NPV 68–100%), and predictive accuracy of these composite clinical predictors for week 16 response outcomes was even higher at week 8 (sensitivity 93–100%; NPV 80–100%). Sensitivity and NPV, as well as specificity and PPV, were generally numerically lower, and never higher, when clinical predictors were considered at week 4 compared with week 8 across all response outcomes, although differences were usually small. Findings were generally consistent across both sets of analyses (the pooled results of baricitinib as monotherapy and those of

Table 2 Predictive properties of five clinical response predictors for ≥ 75% improvement in Eczema Area and Severity Index (EASI 75) or ≥ 4-point improvement in Itch Numeric Rating Scale (Itch NRS ≥ 4) composite response outcome at week 16 with baricitinib 4 mg once daily[a]

Predictor	Week	Sensitivity	Specificity	PPV	NPV
Pooled monotherapy studies (BREEZE-AD1 and BREEZE-AD2)					
EASI 50	2	0.67	0.70	0.49	0.83
	4	0.83	0.65	0.51	0.90
	8	0.87	0.71	0.57	0.92
vIGA-AD ≤ 2	2	0.57	0.76	0.51	0.80
	4	0.75	0.74	0.55	0.87
	8	0.83	0.79	0.63	0.91
Itch NRS ≥ 3	2	0.36	0.87	0.55	0.76
	4	0.56	0.83	0.59	0.81
	8	0.65	0.87	0.68	0.85
EASI 50 or Itch NRS ≥ 3	2	0.73	0.65	0.47	0.85
	4	0.91	0.61	0.50	0.94
	8	0.95	0.69	0.57	0.97
vIGA-AD ≤ 2 or Itch NRS ≥ 3	2	0.68	0.68	0.48	0.83
	4	0.92	0.68	0.56	0.95
	8	0.97	0.74	0.62	0.98
Combination therapy study (BREEZE-AD7)					
EASI 50	2	0.68	0.40	0.64	0.44
	4	0.85	0.42	0.70	0.64
	8	0.91	0.51	0.75	0.79
vIGA-AD ≤ 2	2	0.53	0.65	0.71	0.47
	4	0.62	0.53	0.68	0.47
	8	0.68	0.63	0.74	0.55
Itch NRS ≥ 3	2	0.54	0.72	0.76	0.50
	4	0.72	0.56	0.72	0.56
	8	0.74	0.65	0.77	0.61
EASI 50 or Itch NRS ≥ 3	2	0.81	0.33	0.65	0.52
	4	0.97	0.30	0.69	0.87
	8	0.99	0.42	0.73	0.95
vIGA-AD ≤ 2 or Itch NRS ≥ 3	2	0.78	0.47	0.70	0.57
	4	0.90	0.35	0.69	0.68
	8	0.93	0.47	0.73	0.80

NPV, negative predictive value; PPV, positive predictive value; vIGA-AD, validated Investigator Global Assessment for Atopic Dermatitis. [a]Analyses used pooled baricitinib monotherapy data from the BREEZE-AD1 and BREEZE-AD2 studies and data for baricitinib in combination with topical corticosteroids from the BREEZE-AD7 study.

Table 3 Predictive properties of five clinical response predictors for ≥ 75% improvement in Eczema Area and Severity Index (EASI 75) response outcome at week 16 with baricitinib 4 mg once daily[a]

Predictor	Week	Sensitivity	Specificity	PPV	NPV
Pooled monotherapy studies (BREEZE-AD1 and BREEZE-AD2)					
EASI 50	2	0.75	0.69	0.42	0.90
	4	0.89	0.63	0.42	0.95
	8	0.93	0.68	0.46	0.97
vIGA-AD ≤ 2	2	0.65	0.75	0.44	0.88
	4	0.81	0.71	0.46	0.93
	8	0.88	0.75	0.51	0.95
Itch NRS ≥ 3	2	0.33	0.84	0.39	0.81
	4	0.51	0.78	0.41	0.84
	8	0.58	0.80	0.46	0.86
EASI 50 or Itch NRS ≥ 3	2	0.77	0.62	0.38	0.90
	4	0.93	0.57	0.39	0.96
	8	0.96	0.64	0.44	0.98
vIGA-AD ≤ 2 or Itch NRS ≥ 3	2	0.74	0.66	0.40	0.89
	4	0.93	0.63	0.43	0.97
	8	0.96	0.67	0.47	0.98
Combination therapy study (BREEZE-AD7)					
EASI 50	2	0.75	0.45	0.56	0.67
	4	0.91	0.40	0.58	0.82
	8	0.96	0.45	0.61	0.93
vIGA-AD ≤ 2	2	0.66	0.72	0.69	0.7
	4	0.74	0.60	0.63	0.71
	8	0.79	0.66	0.68	0.78
Itch NRS ≥ 3	2	0.47	0.59	0.51	0.55
	4	0.64	0.41	0.50	0.56
	8	0.68	0.50	0.55	0.63
EASI 50 or Itch NRS ≥ 3	2	0.81	0.29	0.51	0.63
	4	0.96	0.22	0.53	0.87
	8	0.98	0.31	0.57	0.95
vIGA-AD ≤ 2 or Itch NRS ≥ 3	2	0.77	0.40	0.54	0.66
	4	0.87	0.26	0.52	0.68
	8	0.92	0.36	0.57	0.84

Itch NRS ≥ 3, ≥ 3-point improvement in Itch Numeric Rating Scale; NPV, negative predictive value; PPV, positive predictive value; vIGA-AD, validated Investigator Global Assessment for Atopic Dermatitis. [a]Analyses used pooled baricitinib monotherapy data from the BREEZE-AD1 and BREEZE-AD2 studies and data for baricitinib in combination with topical corticosteroids from the BREEZE-AD7 study.

baricitinib in combination with TCS). However, the composite clinical predictor EASI 50 or Itch NRS ≥ 3 at weeks 4 and 8 appeared to have higher sensitivity and NPV than the composite clinical predictor vIGA-AD ≤ 2 or Itch NRS ≥ 3 at weeks 4 and 8, respectively, for all response outcomes when baricitinib was used in combination with TCS, whereas both composite clinical predictors seemed to perform similarly in the monotherapy analyses (Tables 2–4). Assessment of clinical predictors at earlier timepoints (week 2) had limited predictive value (Tables 2–4).

For patients achieving an EASI 50 or Itch NRS ≥ 3 at week 8, week 16 EASI 75 response rates were 44.4% and 56.5% with baricitinib, as monotherapy and in combination with TCS, respectively, and higher than the respective Itch NRS ≥ 4 response rates at week 16 (32.3% and 47.8%) in these patients (Figure 1). Responder rates for this predictor combination were highest when clinical response was defined as EASI 75 or Itch NRS ≥ 4 at week 16 (57.3% and 72.8% of patients, respectively). In both datasets, for patients with a vIGA-AD ≤ 2 or Itch NRS ≥ 3 at week 8, week 16 EASI 75 response rates were 46.6% and 57.0%, respectively, and week 16 Itch NRS ≥ 4 response rates were 35.6% and 50.0%, respectively; 61.9% and 73.3% of patients, respectively, achieved the composite response outcome EASI 75 or Itch NRS ≥ 4 at week 16 (Figure 2). For both response outcome combinations, using week 4 clinical predictors yielded similar findings to those at week 8.

Considerably fewer non-early responders, defined using any clinical predictor at week 4 or 8, achieved a response outcome at week 16. A large separation of responder rates between patients with vs. without an early week-4 or, more so, week-8 response according to both composite clinical predictors was observed throughout the graphs (Figures 1 and 2). However, 32% and 20% of these non-early responders achieved the composite response outcome EASI 75 or Itch NRS ≥ 4 at week 16 when vIGA ≤ 2 or Itch NRS ≥ 3 at week 4 or 8, respectively, was the composite clinical predictor in the combination with TCS analysis.

Discussion

Combining data from multiple clinical trials evaluating baricitinib 4 mg for moderate-to-severe AD,[2,3] we identified early clinical predictors of later treatment outcomes. These early predictors were measured at weeks 4 and 8, and include a

Table 4 Predictive properties of five clinical response predictors for ≥ 4-point improvement in Itch Numeric Rating Scale (Itch NRS ≥ 4) response outcome at week 16 with baricitinib 4 mg once daily[a]

Predictor	Week	Sensitivity	Specificity	PPV	NPV
Pooled monotherapy studies (BREEZE-AD1 and BREEZE-AD2)					
EASI 50	2	0.60	0.63	0.25	0.88
	4	0.81	0.58	0.29	0.94
	8	0.81	0.61	0.30	0.94
vIGA-AD ≤ 2	2	0.51	0.69	0.26	0.87
	4	0.70	0.65	0.30	0.91
	8	0.77	0.68	0.34	0.93
Itch NRS ≥ 3	2	0.53	0.87	0.47	0.90
	4	0.79	0.82	0.48	0.95
	8	0.91	0.84	0.54	0.98
EASI 50 or Itch NRS ≥ 3	2	0.72	0.59	0.27	0.91
	4	0.91	0.53	0.29	0.96
	8	0.93	0.59	0.32	0.98
vIGA-AD ≤ 2 or Itch NRS ≥ 3	2	0.67	0.62	0.27	0.90
	4	0.93	0.59	0.32	0.98
	8	0.98	0.63	0.36	0.99
Combination therapy study (BREEZE-AD7)					
EASI 50	2	0.64	0.34	0.39	0.59
	4	0.86	0.33	0.46	0.79
	8	0.91	0.36	0.48	0.86
vIGA-AD ≤ 2	2	0.45	0.54	0.39	0.60
	4	0.59	0.46	0.42	0.63
	8	0.64	0.49	0.45	0.67
Itch NRS ≥ 3	2	0.70	0.73	0.63	0.79
	4	0.93	0.60	0.60	0.93
	8	0.95	0.66	0.65	0.96
EASI 50 or Itch NRS ≥ 3	2	0.84	0.30	0.44	0.74
	4	1.00	0.22	0.46	1.00
	8	1.00	0.28	0.48	1.00
vIGA-AD ≤ 2 or Itch NRS ≥ 3	2	0.84	0.42	0.49	0.80
	4	0.95	0.30	0.47	0.91
	8	0.98	0.36	0.50	0.96

EASI 50, ≥ 50% reduction from baseline in Eczema Area and Severity Index score; NPV, negative predictive value; PPV, positive predictive value; vIGA-AD, validated Investigator Global Assessment for Atopic Dermatitis. [a]Analyses used pooled baricitinib monotherapy data from the BREEZE-AD1 and BREEZE-AD2 studies and data for baricitinib in combination with topical corticosteroids from the BREEZE-AD7 study.

variety of physician-assessed clinical scores and patient-reported outcomes (PROs), either alone or in combination. The clinical response at week 16 was defined using a generally accepted single or composite measure. Composite early predictors, taking into account both skin inflammation and itch improvement, captured the overall treatment benefit at week 16 more accurately than any single variable alone. Furthermore, we demonstrate that predictions of treatment response are most accurate 8 weeks after initiation of treatment, providing a tool to identify patients who are unlikely to reach defined treatment responses. Additional analyses (data not shown) using vIGA-AD 0,1 as a single or part of a composite response outcome (vIGA-AD 0,1 or Itch NRS ≥ 4) confirmed our findings.

Patients with moderate-to-severe AD for whom topical therapies have not provided adequate relief have a limited number of approved and off-label systemic therapy options available to them.[5,8] Identification of clinical parameters that reliably predict a response to systemic therapy could help both the patient and the physician. The patient may be more likely to agree to initiate a new therapy, and the physician is assisted in minimizing exposure to drugs that are not providing an adequate response.[6] Furthermore, facilitating an early 'go or stop' decision can help reduce healthcare costs in a condition that usually requires long-term therapy.

Linking well-accepted and clinically meaningful[9–11] study endpoints (i.e. EASI 75 and Itch NRS ≥ 4) 16 weeks after treatment initiation to parameters that document early changes in disease severity (e.g. EASI 50, NRS ≥ 3, vIGA-AD score ≤ 2), we identified the composite clinical predictors EASI 50 or Itch NRS ≥ 3, and vIGA-AD ≤ 2 or Itch NRS ≥ 3, as the most reliable clinical measures on which to base real-world treatment decisions. We included measures of both skin improvement (physician-assessed outcomes) and symptomatic relief (PROs) in our clinical predictors and response outcomes because both are important treatment goals.[12] That the composite clinical predictors were the best predictors of the evaluated objective and subjective response outcomes at 16 weeks highlights the value of considering PROs, as well as the established physician-reported outcomes, when evaluating responses to treatment in patients with AD. The importance of including PROs as clinical predictors was also noted in another predictor analysis that identified pain reduction as a valid indicator of response to baricitinib in patients with rheumatoid arthritis.[13]

Based on sensitivity and NPV, assessment of predictors at weeks 4 or 8 yielded the highest predictive accuracy. In this respect, the week 8 timepoint provided additional gains compared with week 4 and little difference from week 12 (data not shown). Of the statistical measures available, we considered sensitivity – which indicates how many of the patients who will benefit from therapy will have an early response – and NPV – which indicates how many patients without an early response are unlikely to ever have a response – to be the most useful for informing the decision of stopping or continuing treatment with baricitinib. Both of these statistical measures are important, as it should be recognized that some patients who do not have an early response will go on to achieve a clinically meaningful response to baricitinib later during therapy, as shown by the PPV and specificity findings. In agreement with our findings, a previous analysis of baricitinib 2 mg in patients with AD and baseline BSA 10–50% who had an inadequate response or intolerance to TCS showed that either a response in skin inflammation (≥ 50% improvement in BSA) or itch (≥ 3-point improvement in Itch NRS) at week 4 or 8 was associated with EASI 75, vIGA-AD 0,1 and ≥ 4-point improvement in Itch NRS at week 16.[14]

The results of our analyses were generally consistent across the two patient groups, showing that the optimal timing of the evaluation and identity of the clinical predictors were the same for baricitinib delivered as monotherapy or in combination with TCS. On the basis of this responder analysis, we recommend that consideration should be given to discontinuing baricitinib treatment in patients with AD who show no evidence of therapeutic benefit after 8 weeks of treatment, while recognizing that a small proportion of these non-early responding patients will go on to benefit from therapy. Likewise, treatment should be continued in those patients who show improvement at this timepoint. Limited skin improvement and key symptom improvement (EASI 50 or Itch NRS ≥ 3) at week 8 is sufficient to predict the well-accepted and clinically meaningful treatment goals of EASI 75 and/or Itch NRS ≥ 4 at week 16. Such 'response-guided therapy' – a concept that is used in the management of some

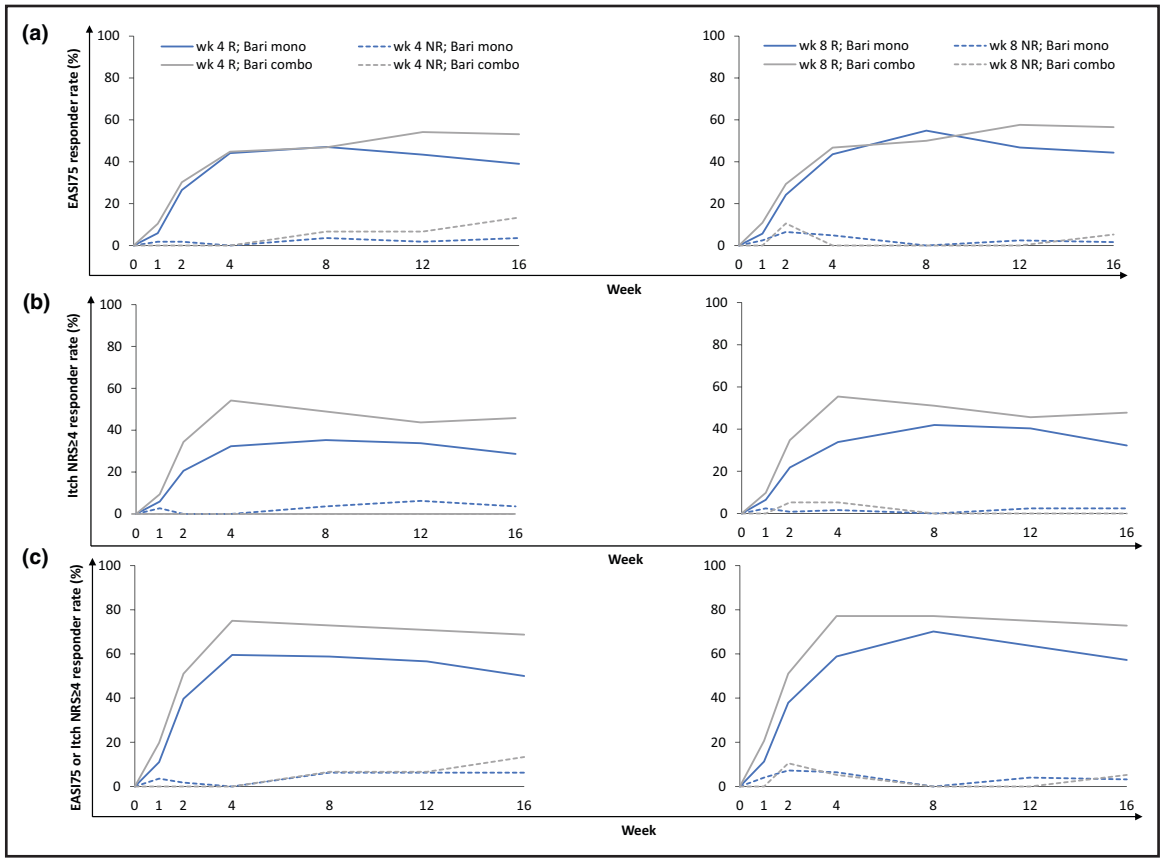

Figure 1 Validation of the combination of ≥ 50% improvement in Eczema Area and Severity Index (EASI 50) or ≥ 3-point improvement in Itch Numeric Rating Scale (Itch NRS ≥ 3) as an early predictor of clinical response. Proportion of EASI 50 or Itch NRS ≥ 3 responders (R, solid lines) and nonresponders (NR, dotted lines) at week (wk) 4 and 8, who achieved (a) EASI 75, (b) Itch NRS ≥ 4 and (c) EASI 75 or Itch NRS ≥ 4 during the first 16 weeks of baricitinib 4 mg (Bari) as monotherapy or in combination with topical corticosteroids (TCS). Data for baricitinib 4 mg as monotherapy (Bari mono; pooled from the BREEZE-AD1 and BREEZE-AD2 studies) or in combination with topical corticosteroids (Bari combo; BREEZE-AD7 study); nonresponder imputation.

other conditions – allows early identification of those patients who are unlikely to respond to a particular treatment and provides the opportunity of exploring other treatment options.[15]

This study has a number of strengths and limitations. Strengths of this analysis are the consistency of the relationship between clinical predictors and response outcomes demonstrated across the different studies and treatment strategies, and the use of well-accepted and mainly validated measures of clinical improvement. Limitations are the lack of long-term efficacy data as well as the potential risk of assessment bias and interobserver variation when applying clinical scores to evaluate disease severity. Areas of future research include evaluation of the clinical predictor model in the real-world setting and identification of novel predictors to optimize response-guided therapy in patients with moderate-to-severe AD.

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Eli Lilly and Company (Indianapolis, IN, USA) was involved in study design, data collection, data analysis, data interpretation, manuscript preparation and publication decisions. All authors had full access to all data in the study and had final responsibility for the decision to submit for publication.

Conflicts of interest

T.B. has acted as speaker, and/or consultant and/or investigator for AbbVie, Almirall, AnaptysBio, Arena Pharmaceuticals Ltd, Asana Biosciences, Astellas Pharma, Bayer Health, BioVerSys, Boehringer Ingelheim, Celgene, Daiichi Sankyo, Dermavant/Roivant, Dermtreat, Domain Therapeutics, DS Pharma, Eli Lilly and Company, Galapagos/MorphoSys, Galderma, Glenmark Pharmaceuticals, GSK, Incyte, Kymab, L'Oréal, LEO Pharma, Menlo Therapeutics, Novartis, Pfizer, Pierre Fabre, RAPT Therapeutics/FLX Bio, Sanofi/Regeneron and UCB; and he is founder of the nonprofit biotech company Davos Biosciences. J.P.T. is an advisor for AbbVie, Almirall, Arena Pharmaceuticals, Aslan Pharmaceuticals, Eli Lilly and Company, LEO Pharma, OM Pharma, Pfizer, Regeneron, Sanofi/Genzyme and UNION Therapeutics; is a speaker for AbbVie, Almirall, Eli Lilly and Company, LEO Pharma, Pfizer,

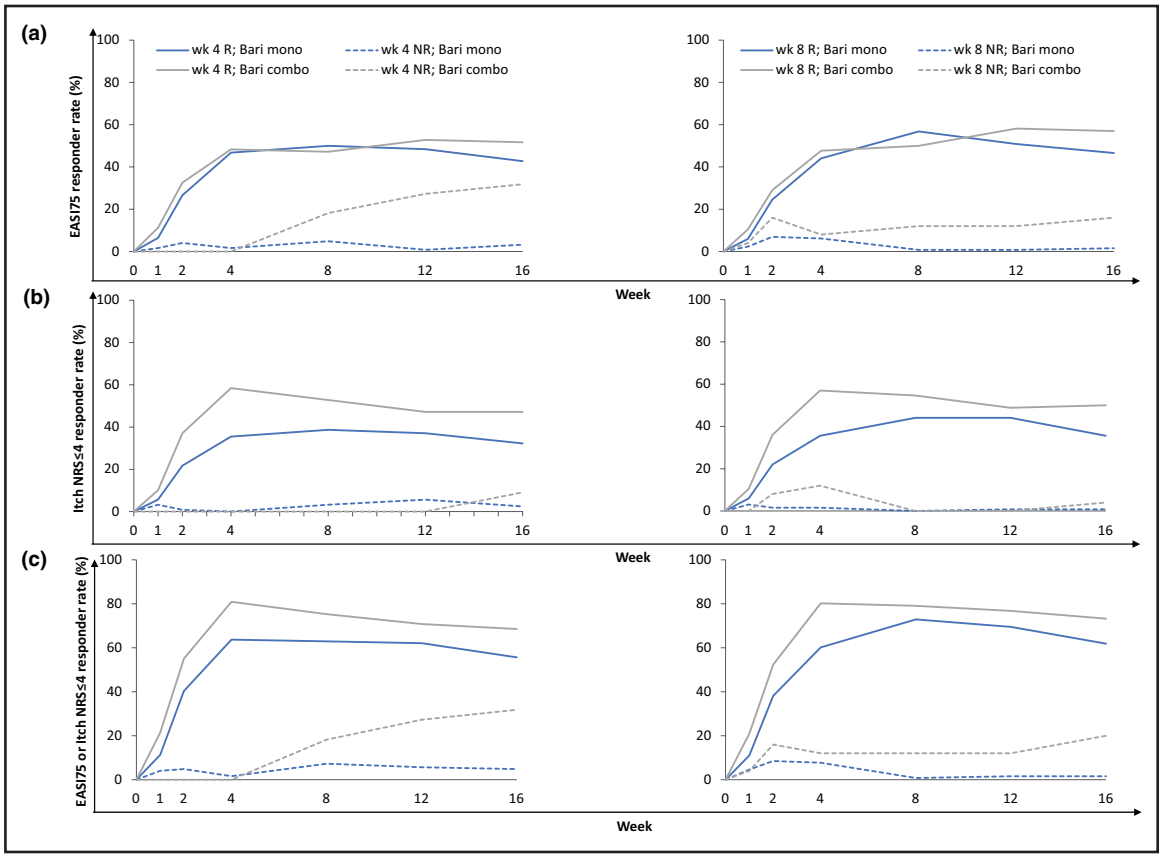

Figure 2 Validation of the combination of validated Investigator Global Assessment for AD (vIGA-AD) score ≤ 2 or ≥ 3-point improvement in Itch Numeric Rating Scale (Itch NRS ≥ 3) as an early predictor of clinical response. Proportion of vIGA-AD ≤ 2 or Itch NRS ≥ 3 responders (R, solid lines) and nonresponders (NR, dotted lines) at week (wk) 4 and 8, who achieved (a) ≥ 75% improvement in Eczema Area and Severity Index (EASI 75), (b) Itch NRS ≥ 4 and (c) EASI 75 or Itch NRS ≥ 4 during the first 16 weeks of baricitinib 4 mg (Bari) as monotherapy or in combination with topical corticosteroids (TCS). Data for baricitinib 4 mg as monotherapy (Bari mono; pooled from the BREEZE-AD1 and BREEZE-AD2 studies) and in combination with TCS (Bari combo; BREEZE-AD7 study); nonresponder imputation.

Regeneron and Sanofi/Genzyme; and has received research grants from Pfizer, Regeneron and Sanofi/Genzyme. A.D.I. is a consultant/speaker for AbbVie, Almirall, Arena, Benevolent AI, LEO Pharma, Lilly, Pfizer and Regeneron. Y.T. has received fees for lectures from Eli Lilly Japan K.K., Kyowa Kirin Co., Ltd., Maruho Co., Ltd., Mitsubishi Tanabe Pharma Corporation, Novartis Pharma K.K., Sanofi K.K., Taiho Pharmaceutical Co., Ltd. and Torii Pharmaceutical Co., Ltd. Y.F.C., L.S., A.S. and E.R. are employees of and shareholders in Eli Lilly and Company. M.J.C. has served as a clinical trial investigator for Astellas Pharma, Atopix, Galapagos NV, Harvey Water Softeners, Hyphens Pharma, Johnson & Johnson, Kymab, LEO Pharma, L'Oréal, Novartis, Oxagen, Perrigo, Pfizer, Reckitt Benckiser, Regeneron and Sanofi Genzyme; and has served as a consultant for Astellas, Atopix Therapeutix Limited, Boots, Dermavant Sciences, Eli Lilly, Galapagos NV, Galderma, Harvey Water Softeners, Hyphens Pharma, Johnson & Johnson, Kymab, LEO Pharma, L'Oréal, Menlo Therapeutics, Novartis, Oxagen, Perrigo, Pfizer Inc., Procter & Gamble, Reckitt Benckiser, Regeneron, Sanofi/Genzyme and UCB.

Data availability

The data that support the findings of this study are available from the corresponding author on reasonable request.

Ethics statement

Not applicable.

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*SOTYKTU was studied in two global, Phase 3, randomised, multi-arm clinical studies: POETYK PSO-1 and PSO-2. **PASI 75 and sPGA 0/1 vs. placebo at Week 16 were co-primary endpoints**. PASI 75 was defined as ≥75% reduction from baseline in the Psoriasis Area and Severity Index. sPGA was defined as sPGA score of 0 or 1 with ≥2-point improvement from baseline. N numbers: PSO-1: SOTYKTU (n=332); apremilast (n=168), placebo (n=166); PSO-2: SOTYKTU (n=511); apremilast (n=254), placebo (n=255). SOTYKTU delivered superior PASI 75 response rates vs placebo (PSO-1: 58.4% vs. 12.7%, p<0.0001; PSO-2: 53.0% vs. 9.4%, p<0.0001) at Week 16, and superior results achieving clear or almost clear skin (sPGA 0/1) vs. placebo (PSO-1: 53.6% vs. 7.2%, p<0.0001; PSO-2: 49.5% vs. 8.6%, p<0.0001) at Week 16 (co-primary endpoints).[2,3]

†Via enzyme inhibition, enzyme induction, or transporter inhibition.[1]

Abbreviations: AE, adverse event; DDI, drug–drug interaction; PASI, Psoriasis Area and Severity Index; sPGA, static Physician's Global Assessment; TYK2, tyrosine kinase 2.

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Bristol Myers Squibb™

Job code: 1787-GB-2300026 Date of preparation: September 2023

SOTYKTU® (deucravacitinib) PRESCRIBING INFORMATION

Great Britain

Consult Summary of Product Characteristics (SmPC) before prescribing. **This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information.**

PRESENTATION: Film-coated tablet containing 6 mg of deucravacitinib.

INDICATION: Treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.

DOSAGE AND ADMINISTRATION: Treatment should be initiated under the guidance and supervision of a physician experienced in the diagnosis and treatment of psoriasis. Posology: 6 mg orally once daily. If a patient shows no evidence of therapeutic benefit after 24 weeks, treatment discontinuation should be considered. The patient's response to treatment should be evaluated on a regular basis. Special populations: *Elderly:* No dose adjustment is required in elderly patients aged 65 years and older. Clinical experience in patients ≥ 75 years is very limited and deucravacitinib should be used with caution in this group of patients. *Renal Impairment:* No dose adjustment is required in patients with renal impairment, including end stage renal disease (ESRD) patients on dialysis. *Hepatic impairment:* No dose adjustment is required in patients with mild or moderate hepatic impairment. Deucravacitinib is not recommended to be used in patients with severe hepatic impairment. *Paediatric population:* The safety and efficacy of deucravacitinib in children and adolescents below the age of 18 years have not yet been established. No data are available. Method of administration: For oral use. Tablets can be taken with or without food. Tablets should be swallowed whole and should not be crushed, cut, or chewed.

CONTRAINDICATIONS: Hypersensitivity to the active substance or to any of the excipients (see SmPC). Clinically important active infections (e.g. active tuberculosis).

WARNINGS AND PRECAUTIONS: Infections: Treatment should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated. Caution should be exercised when considering the use in patients with a chronic infection or a history of recurrent infection. Patients treated with deucravacitinib should be instructed to seek medical advice if signs or symptoms suggestive of an infection occur. If a patient develops a clinically important infection or is not responding to standard therapy, monitor carefully and deucravacitinib should not be given until the infection resolves. Pre-treatment evaluation for tuberculosis (TB): Prior to initiating treatment with deucravacitinib, patients should be evaluated for TB infection. Deucravacitinib should not be given to patients with active TB. Treatment of latent TB should be initiated prior to administering deucravacitinib. Anti-TB therapy should be considered prior to initiation of deucravacitinib in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Patients receiving deucravacitinib should be monitored for signs and symptoms of active TB. Malignancies*: Malignancies, including lymphomas and non-melanoma skin cancer (NMSC), were observed in clinical studies with deucravacitinib. Limited clinical data are available to assess the potential relationship of exposure to deucravacitinib and the development of malignancies. Long-term safety evaluations are ongoing. The risks and benefits of deucravacitinib treatment should be considered prior to initiating patients**. Major adverse cardiovascular events (MACE), deep venous thrombosis (DVT) and pulmonary embolism (PE)*: An increased risk was not observed in clinical trials with deucravacitinib. Long-term safety evaluations are ongoing. The risks and benefits of deucravacitinib treatment should be considered prior to initiating patients**. Immunisations: Consider completion of all age-appropriate immunisations according to current immunisation guidelines prior to initiating therapy. Use of live vaccines in patients being treated with deucravacitinib should be avoided. Excipients: Contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose galactose malabsorption should not take this medicinal product. Contains less than 1 mmol of sodium (23 mg) per tablet, essentially 'sodium-free'. *serious. **It is not known whether tyrosine kinase 2 (TYK2) inhibition may be associated with the adverse reactions of Janus Kinase (JAK) inhibition. In a large randomised active-controlled study of a JAK inhibitor in rheumatoid arthritis (RA) patients 50 years and older with at least one additional cardiovascular risk factor, a higher rate of malignancies (particularly lung cancer, lymphoma and NMSC), a higher rate of MACE (defined as cardiovascular death, non-fatal myocardial infarction and non-fatal stroke), and a dose dependent higher rate of venous thromboembolism (including DVT and PE) were observed with a JAK inhibitor compared to TNF inhibitors.

INTERACTIONS: Deucravacitinib does not have any known clinically relevant drug interactions. Refer to SmPC for full details.

PREGNANCY AND LACTATION: Pregnancy: There is a limited amount of data on the use of deucravacitinib in pregnant women. As a precautionary measure, it is preferable to avoid the use of deucravacitinib during pregnancy. Breast-feeding: It is unknown whether deucravacitinib/metabolites are excreted in human milk. A risk to the newborns/infants by breast-feeding cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from deucravacitinib therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman. Fertility: The effect of deucravacitinib on human fertility has not been evaluated.

UNDESIRABLE EFFECTS: The most commonly reported adverse reaction is upper respiratory infections (18.9%), most frequently nasopharyngitis. The longer-term safety profile of deucravacitinib was similar and consistent with previous experience. Very common (≥ 1/10): Upper respiratory infections*** (including nasopharyngitis, upper respiratory tract infection, viral upper respiratory tract infection, pharyngitis, sinusitis, acute sinusitis, rhinitis, tonsillitis, peritonsillar abscess, laryngitis, tracheitis, and rhinotracheitis). Common (≥ 1/100 to < 1/10): Herpes simplex infections*** (including oral herpes, herpes simplex, genital herpes, and herpes viral infection), Oral ulcers (including aphthous ulcer, mouth ulceration, tongue ulceration, and stomatitis), Acneiform rash (including acne, dermatitis acneiform, rash, rosacea, pustule, rash pustular, and papule), Folliculitis and Blood creatine phosphokinase increased. Uncommon (≥ 1/1,000 to < 1/100): Herpes zoster***. Refer to SmPC for full details on adverse reactions.

***serious adverse drug reaction

LEGAL CATEGORY: POM

MARKETING AUTHORISATION NUMBER and BASIC NHS PRICE: PLGB 15105/0179: Carton of 28 film-coated tablets 6 mg NHS price: £690.00; Carton of 84 film-coated tablets 6 mg NHS price: £2070.00.

MARKETING AUTHORISATION HOLDER: Bristol-Myers Squibb Pharma EEIG, Plaza 254, Blanchardstown Corporate Park 2, Dublin 15, D15 T867, Ireland.

FOR FURTHER INFORMATION CONTACT:

medical.information@bms.com or 0800 731 1736 (Great Britain).

DATE OF PREPARATION: May 2023

ADDITIONAL INFORMATION AVAILABLE ON REQUEST

Approval code: 1787-GB-2300080

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Northern Ireland / Ireland

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***serious adverse drug reaction

LEGAL CATEGORY: POM

MARKETING AUTHORISATION NUMBER and BASIC NHS PRICE: EU/1/23/1718/006: Carton of 28 film-coated tablets 6 mg NHS price: £690.00.

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DATE OF PREPARATION: June 2023

ADDITIONAL INFORMATION AVAILABLE ON REQUEST

Approval code: 1787-IE-2300001

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