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ORIGINAL RESEARCH

Durability of Response to Abrocitinib in Patients with Moderate-to-Severe Atopic Dermatitis After Treatment Discontinuation in a Phase 2b Trial

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ABSTRACT

Introduction: Multiple clinical trials showed that 12 weeks of abrocitinib monotherapy was safe and effective for the treatment of moderate-to-severe atopic dermatitis (AD). The reversibility of pharmacologic activity after abrocitinib discontinuation was not described.

Methods: This post hoc analysis used data from a phase 2b study to evaluate maintenance of disease control during a 4-week drug-free follow-up period in patients with moderate-to-severe AD treated with once-daily abrocitinib (200 mg/100 mg) or placebo for 12 weeks. Proportions of patients who achieved and maintained 50% or 75% improvement in Eczema Area and Severity Index (EASI-50/EASI-75), an Investigator's Global Assessment (IGA) score of 0/1, or at least a 4-point improvement in the pruritus numeric rating scale (pruritus NRS4) were determined. Biomarkers of Janus kinase inhibition and AD disease were measured in blood samples.

Results: Among week 12 responders to abrocitinib 200 mg, 77.4%, 42.3%, 21.1%, and 42.9% maintained their EASI-50, EASI-75, IGA, and pruritus NRS4 response at week 16; corresponding proportions of week 12 responders maintaining response to abrocitinib 100 mg were 51.9%, 35.0%, 33.3%, and 43.5%, respectively. Four weeks after abrocitinib discontinuation, all AD biomarkers reverted toward

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baseline levels, with high-sensitivity C-reactive protein and eosinophil percentage demonstrating the most complete recovery in patients treated with abrocitinib versus placebo.
Conclusion: Abrocitinib discontinuation resulted in rapid reversal of disease control consistent with reversal of suppression of pharmacodynamic and AD-specific biomarkers during the drug-free follow-up period. Maintenance of response was inversely related to the threshold of improvement. Patients with moderate-to-severe AD using continuous abrocitinib therapy would likely have the best long-term outcomes.
Trial Registration: ClinicalTrials.gov identifier NCT02780167.

Keywords: Abrocitinib; Atopic dermatitis; Biomarker; Discontinuation; Eczema; Pruritus

Key Summary Points

In this clinical study, patients with eczema who were treated once daily with abrocitinib for 12 weeks showed improvement in the signs and symptoms of their disease.

This report looked at how long the beneficial effect of treatment lasted in the 4-week period after the drug was stopped.

The results of this analysis showed that the signs and symptoms of the disease returned quickly and suggest that patients need to take the drug continuously to keep their eczema under control.

INTRODUCTION

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disease characterized by dry, inflamed, itchy skin [1–4]. The prevalence of AD was reported to be between 2% and 10% in adults and between 15% and 30% in children in Western countries [1, 2].

Abrocitinib is an oral, once-daily, selective Janus kinase 1 (JAK1) inhibitor approved for the treatment of adults [5–8] and adolescents [5, 6] with moderate-to-severe AD. In a phase 2b study (NCT02780167), abrocitinib 200 mg or 100 mg showed clinically meaningful improvement in Investigator's Global Assessment (IGA), 90% improvement on the Eczema Area and Severity Index (EASI-90), and a 4-point or greater improvement on the baseline pruritus numeric rating scale (pruritus NRS4) at week 12 [9, 10]. The efficacy and safety of once-daily abrocitinib (100 mg or 200 mg) in patients with moderate-to-severe AD were confirmed in three phase 3 studies (JADE MONO-1, NCT03349060; JADE MONO-2, NCT03575871; and JADE COMPARE, NCT03720470) [11–13].

Abrocitinib exerts pharmacologic action through reversible inhibition of JAK1 and is eliminated rapidly (mean $t_{1/2}$ 2.8–5.2 h after 10 days of once- or twice-daily administration) [14]. Therefore, associated pharmacologic effects are expected to diminish following treatment discontinuation. The durability of the response after discontinuation of abrocitinib was not reported. The objective of this analysis was to characterize the durability of response and the changes in pharmacodynamic and AD-specific biomarkers in the phase 2b study (NCT02780167) after abrocitinib discontinuation.

METHODS

Study Design and Endpoints

A phase 2b, multicenter, randomized, double-blinded, placebo-controlled, parallel-group study was conducted between April 15, 2016, and April 4, 2017, at 58 centers in Australia, Canada, Germany, Hungary, and the USA (NCT02780167) to determine the efficacy and safety of once-daily abrocitinib (200 mg, 100 mg, 30 mg, or 10 mg) for patients with moderate-to-severe AD. Patients were randomly assigned 1:1:1:1:1 to receive abrocitinib (200, 100, 30, or 10 mg) or placebo once daily for 12 weeks, followed by 4 weeks of follow-up after discontinuation of study medication [9, 10].

Permitted concomitant AD medications were oral antihistamines and sponsor-provided emollient and sunscreen. The current analysis reports data for the placebo and abrocitinib 100- and 200-mg groups only.

The study was conducted in accordance with the Declaration of Helsinki, all International Council for Harmonization Good Clinical Practice Guidelines, and all local regulatory requirements following approval from the institutional review boards (IRBs) or ethics committees (ECs) at each study site. All patients provided written informed consent [9, 10]. A list of all IRBs and ECs is provided in the Supplementary Material.

Eligible patients were those aged 18–75 years with moderate-to-severe AD (IGA score $\geq$ 3, EASI score $\geq$ 12, percentage of affected body surface area $\geq$ 10) and an inadequate response or intolerance to topical medication [9].

Outcome Measures

In patients who achieved 50% or 75% improvement in EASI (EASI-50, EASI-75), IGA response (clear or almost clear and a 2-point or greater reduction from baseline), or pruritus NRS4 response at week 12, a post hoc analysis was performed to determine the proportions of patients who maintained EASI-50, EASI-75, IGA response, and pruritus NRS4 at week 16 (i.e., 4 weeks after treatment discontinuation). All patients with reported outcome measures at week 16 were analyzed. The proportions of patients who experienced worsened EASI and pruritus NRS scores, which were defined as exceeding baseline values by at least two intrapatient standard deviations, were also determined.

Biomarkers

Serum biomarkers were evaluated for the purpose of corroborating the findings on the outcome measures. Blood samples were collected during abrocitinib treatment and after discontinuation at week 12 to evaluate biomarkers of AD (serum interleukin [IL]-31 and thymus and activation-regulated chemokine [TARC] concentrations and blood eosinophil percentage). The concentration of high-sensitivity C-reactive protein (hs-CRP), which reflects both the pharmacodynamics of JAK inhibition and AD severity, was also evaluated [15–17].

The biomarker analysis used data only from patients who received at least one dose of study drug in the placebo and abrocitinib 200-mg and 100-mg groups. Descriptive analyses were performed using R 3.4.4 (R Core Team, Vienna, Austria).

RESULTS

Baseline Characteristics

Of the 267 patients included in the phase 2b study, 164 in the full analysis set were treated with abrocitinib 200 mg (n = 54), abrocitinib 100 mg (n = 55), or placebo (n = 55) [9, 10] and were included in this post hoc analysis. The mean age for patients receiving placebo, abrocitinib 100 mg, and abrocitinib 200 mg was 42.6, 41.1, and 38.7 years, respectively, and the median disease duration was 25.6, 23.8, and 19.6 years, respectively (Table 1) [9, 10]. Most participants were White (70.1%) and had moderate disease (IGA-3, 59.1%); 52.1% were women [9, 10].

Maintenance of Response After Discontinuation of Abrocitinib

At week 12, there were 49 IGA responders. Of those, 3 (6.1%) received placebo, 16 (32.7%) received abrocitinib 100 mg, and 21 (42.9%) received abrocitinib 200 mg. (The remaining 9 patients were treated with abrocitinib 10 mg or 30 mg and are not analyzed here.) Maintenance of response at week 16 was observed in 100% (2/2), 33.3% (5/15), and 21.1% (4/19) of the patients receiving placebo, abrocitinib 100 mg, and abrocitinib 200 mg, respectively, who had data at that visit. Maintenance rates for EASI-50 or EASI-75 at week 16 were higher than those of IGA response, with the highest maintenance rates observed for EASI-50 (Fig. 1; Table 2).

At week 12, there were 91 pruritus NRS4 responders. Of those, 13 (14.3%) received

Table 1 Baseline demographics and clinical characteristics [9]

	Abrocitinib 200 mg	Abrocitinib 100 mg	Placebo
Safety analysis set, *N*	55	56	56
Age, mean (SD), years	38.7 (17.6)	41.1 (15.6)	42.6 (15.1)
Male sex, *n* (%)	28 (50.9)	31 (55.4)	21 (37.5)
Race, *n* (%)			
White	37 (67.3)	40 (71.4)	40 (71.4)
Black	13 (23.6)	7 (12.5)	10 (17.9)
Asian	5 (9.1)	8 (14.3)	4 (7.1)
Other	0	1 (1.8)	2 (3.6)
Disease duration, median (range), years	19.6 (1.9–68.8)	23.8 (1.1–66.7)	25.6 (1.1–67.1)
Full analysis set, *N*	54	55	55
IGA, *n* (%)			
Moderate (3)	34 (63.0)	29 (52.7)	34 (61.8)
Severe (4)	20 (37.0)	26 (47.3)	21 (38.2)
EASI, mean (SD)	24.6 (13.5)	26.7 (11.8)	25.4 (12.9)

EASI Eczema Area and Severity Index, *IGA* Investigator's Global Assessment, *SD* standard deviation

placebo, 25 (27.5%) received abrocitinib 100 mg, and 28 (30.8%) received abrocitinib 200 mg. Maintenance of response at week 16 was observed in 83.3% (5/6), 43.5% (10/23), and 42.9% (9/21), respectively, of the patients who had data at that visit (Table 2).

Maintenance of Response Below Predose Baseline

Most patients who achieved a response at week 12 maintained EASI and pruritus NRS scores below baseline at week 16. This includes all week 12 responders who received abrocitinib 200 mg and 80.0% of EASI-75 responders (16/20) and 87.0% of pruritus NRS4 responders (20/23) who received abrocitinib 100 mg.

Worsening of Response After Treatment Discontinuation

Worsening of EASI and pruritus NRS scores at week 16 was defined as a score increase over the week 12 values by at least two baseline intrapatient standard deviations (EASI, ≥ 14; pruritus NRS, ≥ 1). Such a worsening was observed in 10.0% of patients (2/20) and 4.3% of patients (1/23) who had attained week 12 EASI-75 and pruritus NRS4, respectively, with abrocitinib 100 mg. None of the patients who had attained week 12 EASI-75 ($n = 26$) or pruritus NRS4 ($n = 21$) with abrocitinib 200 mg experienced such a worsening.

Assessment of Biomarkers After Discontinuation of Abrocitinib

On the basis of the changes from baseline, hs-CRP was more sensitive to abrocitinib treatment than to placebo. Throughout the 12-week dosing period, the median serum concentration of hs-CRP was the lowest for abrocitinib 200 mg, followed by abrocitinib 100 mg, while it was relatively unchanged for placebo (Supplementary Fig. 1). At week 12, the median percentage changes from baseline in hs-CRP serum concentration were − 41.2% (abrocitinib 200 mg),

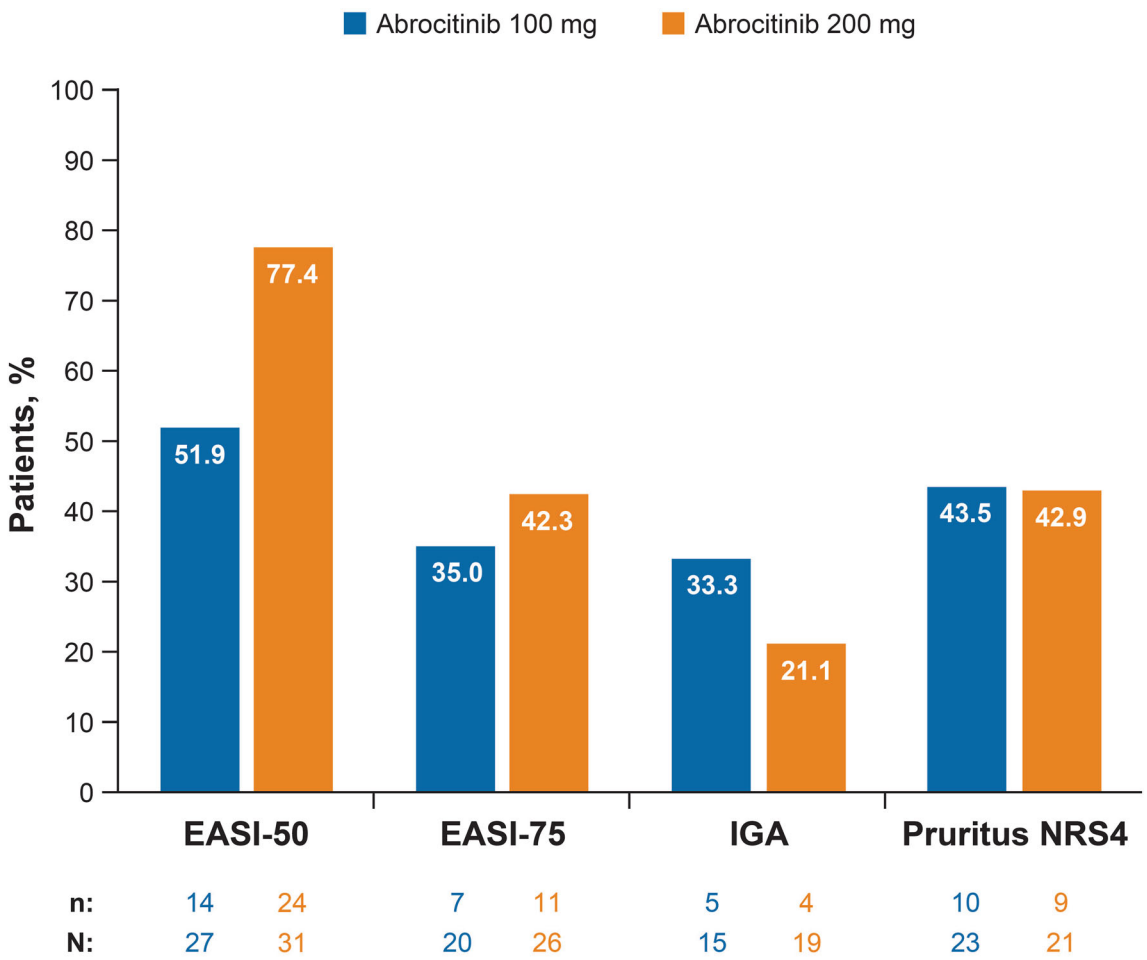

Fig. 1 Proportions of week 12 EASI or pruritus NRS4 responders who maintained response at week 16. EASI-50/EASI-75, 50% or 75% improvement in EASI; IGA response, IGA response of clear (0) or almost clear (1); pruritus NRS4, 4-point or greater improvement in pruritus NRS from baseline. *EASI* Eczema Area and Severity Index, *IGA* Investigator's Global Assessment 0/1, *pruritus NRS4* pruritus numerical rating scale, *n* week 12 responders who maintained the response at week 16, *N* week 12 responders who were evaluable at week 16 (i.e., week 12 responders who maintained and who did not maintain the response at week 16)

– 53.0% (abrocitinib 100 mg), and 36.4% (placebo).

Throughout the 12-week dosing period, the median levels of IL-31, eosinophil percentage, and TARC concentration were lower in patients who received abrocitinib 200 mg than in patients who received abrocitinib 100 mg or placebo (Supplementary Fig. 1). At week 12, all three treatment groups had decreases in serum levels of these biomarkers from baseline. The median percentage change (decrease) from baseline was particularly marked for abrocitinib 200 mg for IL-31, and for both abrocitinib dose levels for eosinophil percentage. At week 12, the median percentage changes from baseline IL-31 concentration were – 73.3% for patients treated with abrocitinib 200 mg, – 35.0% for patients treated with abrocitinib 100 mg, and 6.2% for patients who received placebo. Those values were – 32.3%, – 19.0%, and – 4.2%, respectively, for eosinophil percentage and – 26.1%, – 12.8%, and – 18.0%, respectively, for TARC concentration.

Four weeks after discontinuation (i.e., at week 16), the median serum concentration of hs-CRP, the biomarker most sensitive to

Table 2 Response to abrocitinib treatment at week 12 and maintenance of response at week 16

	Responders at week 12, *n* (%)	Maintained response at week 16, *n*	Did not maintain response at week 16, *n*	Total assessed for response maintenance, *n*	Maintained response at week 16, %
EASI-50 ($N = 109$)[a]					
Placebo	14 (12.8)	8	0	8	100
Abrocitinib 100 mg	30 (27.5)	14	13	27	51.9
Abrocitinib 200 mg	38 (34.9)	24	7	31	77.4
EASI-75 ($N = 75$)[a]					
Placebo	8 (10.7)	6	1	7	85.7
Abrocitinib 100 mg	22 (29.3)	7	13	20	35.0
Abrocitinib 200 mg	31 (41.3)	11	15	26	42.3
IGA ($N = 49$)[a]					
Placebo	3 (6.1)	2	0	2	100.0
Abrocitinib 100 mg	16 (32.7)	5	10	15	33.3
Abrocitinib 200 mg	21 (42.9)	4	15	19	21.1
Pruritus NRS4 ($N = 91$)[a]					
Placebo	13 (14.3)	5	1	6	83.3
Abrocitinib 100 mg	25 (27.5)	10	13	23	43.5
Abrocitinib 200 mg	28 (30.8)	9	12	21	42.9

EASI-50, EASI-75 50% and 75% improvement in the Eczema Area and Severity Index, respectively, *IGA* Investigator's Global Assessment, *pruritus NRS4* 4-point or greater improvement in baseline pruritus numeric rating scale score
[a]The number of total responders at week 12 includes patients who received abrocitinib 10 mg and 30 mg

abrocitinib treatment, increased for both 200-mg and 100-mg dosages (reaching − 16.8% and − 12.8% median percentage change from baseline, respectively), which represents a substantial increase from week 12. In contrast, the median serum concentration of hs-CRP in the placebo group at week 16 was relatively unchanged from week 12, with the same median percentage change from baseline (36.4%).

IL-31 serum concentration, eosinophil percentage, and TARC serum concentration also increased, approaching baseline levels within 4 weeks after discontinuation of both abrocitinib dosages (Supplementary Fig. 1). At week 16, the median percentage changes from baseline for IL-31 were − 20.9% (abrocitinib 200 mg), − 42.7% (abrocitinib 100 mg), and − 6.2% (placebo). For eosinophil percentage, those values were − 7.4%, − 1.1%, and 4.0%, respectively, and for TARC, − 4.8%, − 16.7%, and − 4.6%, respectively (Supplementary Fig. 1).

DISCUSSION

As measured by thresholds of clinically meaningful changes in skin clearance (EASI-75 or IGA response) and itch relief (pruritus NRS4), most patients showed a reversal of response 4 weeks after discontinuation of abrocitinib. Overall, the maintenance of response was inversely related to the stringency of the endpoint. All EASI-75 and pruritus NRS4 responders who received abrocitinib 200 mg and nearly all EASI-75 and pruritus

NRS4 responders who received abrocitinib 100 mg maintained disease activity below baseline. Some patients had week 16 values exceeding baseline but no rebound, which was defined as exceeding baseline scores by two or more standard deviations. These results indicate that discontinuation of abrocitinib was associated with rapid reversal of disease control and suggest that patients may experience maximum clinical benefit when abrocitinib is used without interruption. Eventual discontinuation of abrocitinib may be possible in patients who achieve sustained disease control, but tapering should not be done prematurely.

The rapid reversal of disease control after discontinuation of abrocitinib is corroborated by the trend of AD biomarkers to revert toward predose baseline levels after the last abrocitinib dose. All four biomarkers in patients with moderate-to-severe AD followed this trend, with the most complete recovery noted with hs-CRP and eosinophil percentage.

This study has several limitations, including the post hoc nature of the analyses and the small sample sizes. The small sample size of responders at week 12 of treatment also precluded our ability to clarify whether changes in biomarker levels are correlated with durability of response. Thus, the data should be interpreted with caution.

CONCLUSION

In this phase 2b study conducted in patients with moderate-to-severe AD, biomarker response to abrocitinib rapidly reversed after treatment discontinuation. However, measures of AD severity remained at or below baseline and did not rebound after discontinuation. Patients with moderate-to-severe AD who are prescribed abrocitinib are likely to receive the best outcome when taking abrocitinib without disruption.

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Data Availability. Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

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