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ORIGINAL RESEARCH

Switching from Dupilumab to Abrocitinib in Patients With Moderate-to-Severe Atopic Dermatitis: A Post Hoc Analysis of Efficacy After Treatment With Dupilumab in JADE DARE

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ABSTRACT

Introduction: Primary results of the JADE DARE trial (NCT04345367) demonstrated that abrocitinib was superior to dupilumab in reducing the signs and symptoms of moderate-to-severe atopic dermatitis (AD). This post hoc analysis evaluated the efficacy and safety of abrocitinib in patients with moderate-to-severe AD who were responders or nonresponders to dupilumab using various definitions of response.
Methods: Data included dupilumab-treated patients from JADE DARE who switched to abrocitinib 200 mg when enrolled in the ongoing JADE EXTEND trial (NCT03422822). For

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this analysis, various response criteria at Week 26 of JADE DARE were defined post hoc based on Investigator's Global Assessment (IGA), Eczema Area and Severity Index (EASI), Peak Pruritus Numerical Rating Scale (PP-NRS), and Dermatology Life Quality Index (DLQI) scores or responses. Efficacy was analyzed at Week 12 of JADE EXTEND based on patients' fulfillment of the various response criteria at Week 26 of JADE DARE. EASI scores and percentage changes from baseline in EASI and PP-NRS at Week 26 in JADE DARE were compared with the corresponding scores and percentage changes at Week 12 in EXTEND. Safety was assessed.

***Results*:** Of 365 dupilumab-treated patients in JADE DARE, 316 were enrolled in JADE EXTEND and 312 received abrocitinib 200 mg. Most dupilumab responders for IGA, EASI, PP-NRS, and DLQI at DARE Week 26 maintained their responses 12 weeks after switching to abrocitinib, while a considerable proportion of IGA, EASI, PP-NRS, or DLQI dupilumab nonresponders gained response after switching to abrocitinib. Lower EASI scores and greater percentage changes from baseline in EASI and PP-NRS scores were observed with abrocitinib at EXTEND Week 12 than with dupilumab at DARE Week 26. No new safety signals were observed.

***Conclusion*:** Abrocitinib 200 mg may be an effective treatment option for patients with moderate-to-severe AD who do not achieve an optimal response with dupilumab treatment.

***Clinical Trial Registration*:** Clinicaltrials.gov: NCT04345367 (JADE DARE) and NCT03422822 (JADE EXTEND).

Keywords: Abrocitinib; Atopic dermatitis; Dupilumab; JAK-1 selective inhibitor; Nonresponders; Responders; Switch

PLAIN LANGUAGE SUMMARY

People with atopic dermatitis (AD) have cracked, dry, itchy, red, and painful skin patches. Those with stronger symptoms that do not respond well to creams or ointments applied directly to the damaged skin are said to have moderate or severe AD. Such patients need to take systemic therapy, either as injections or by mouth. Dupilumab, an injectable medicine, was the first systemic therapy approved for moderate or severe AD. Abrocitinib is another approved systemic therapy for moderate or severe AD that works in a different way and is taken by mouth. Currently, we do not know much about patients who had a weak response to dupilumab and switched to abrocitinib. In the JADE DARE clinical trial, participants could take either abrocitinib or dupilumab. After 26 weeks, they could enroll in another study, JADE EXTEND, where they could only take abrocitinib as systemic treatment. Here, we evaluated people who took dupilumab in JADE DARE and switched to abrocitinib in JADE EXTEND to see how well abrocitinib worked in patients who did not respond well to dupilumab treatment. We found that many patients who did not respond well to dupilumab responded strongly to abrocitinib. Most patients who responded well to dupilumab still retained their good response after switching to abrocitinib treatment. Together, these results show that abrocitinib can be a suitable alternative for people with moderate-to-severe AD who do not respond well to dupilumab.

Key Summary Points

Why carry out this study?

Abrocitinib 200 mg was superior to dupilumab in reducing the signs and symptoms of moderate-to-severe atopic dermatitis (AD) over 2–4 weeks in the primary results of the head-to-head JADE DARE trial.

Patients who do not respond to dupilumab could benefit from switching to abrocitinib; however, the decision to switch may be complicated by the lack of a standard definition of response, varied response perception from patient to patient, and paucity of data on patients who switched from dupilumab to abrocitinib.

This post hoc analysis evaluated the efficacy and safety of abrocitinib in patients with moderate-to-severe AD who were responders or nonresponders to dupilumab based on various definitions of response.

What was learned from the study?

Most dupilumab responders at Week 26 of JADE DARE maintained their responses 12 weeks after switching to abrocitinib, while a considerable proportion of dupilumab nonresponders gained a response after the switch.

The safety profile of abrocitinib after switching from dupilumab was consistent with that of previous safety analyses.

If clinically appropriate and permitted by local product information, abrocitinib 200 mg may be an effective and well-tolerated alternative for patients with moderate-to-severe AD who do not respond optimally to dupilumab treatment or who experience dupilumab-related conjunctivitis.

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.27862191.

INTRODUCTION

Systemic therapies may be necessary when topical agents or phototherapy are insufficient to adequately treat patients with moderate-to-severe atopic dermatitis (AD) [1–3]. Abrocitinib, an oral, once-daily Janus kinase (JAK) 1-selective inhibitor, and dupilumab, an injectable interleukin-4 receptor α antagonist, are both strongly recommended by international AD guidelines for use in patients with moderate-to-severe AD who require systemic treatment [4, 5]. In the phase 3, head-to-head randomized trial JADE DARE (NCT04345367) [6], abrocitinib previously demonstrated superiority to dupilumab in reducing the signs and symptoms of moderate-to-severe AD within 2–4 weeks, with sustained improvements observed through 16 weeks, although between-group differences decreased over the 26-week treatment period. While both abrocitinib and dupilumab are efficacious treatment options for AD [5], in clinical practice, patients initially treated with dupilumab may switch to abrocitinib because of intolerance, inadequate efficacy, or preference for oral therapy. Assessing the benefits and risks of this switch may be complicated by several factors: the absence of standard definitions for optimal, partial, or nonresponse; variations in clinician perception of response depending on individual patient expectations; lack of recommendation for this switch in current guidelines; and paucity of data on patients who switched from dupilumab to abrocitinib.

Results from several recent analyses have suggested that switching from dupilumab to a JAK inhibitor may have clinical benefits in patients with moderate-to-severe AD. A recent post hoc analysis of data from abrocitinib phase 2b (NCT02780167) and multiple phase 3 trials from the JADE clinical trial program (JADE MONO-1 [NCT03349060], JADE MONO-2 [NCT03575871], JADE REGIMEN [NCT03627767], and JADE EXTEND

[NCT03422822]) suggested that previous exposure to oral systemic or biologic therapies, including dupilumab, did not affect efficacy of abrocitinib in patients with moderate-to-severe AD [7]. Another post hoc analysis of data from JADE COMPARE (NCT03720470) and JADE EXTEND (NCT03422822) evaluated dupilumab responders and nonresponders who switched to abrocitinib 200 mg and 100 mg and found that previous dupilumab response status did not seem to impact the subsequent response to abrocitinib [8]. Similarly, a 16-week interim analysis of an open-label extension study (NCT04195698) assessed the efficacy of upadacitinib, another oral selective JAK inhibitor, in patients who had previously received dupilumab and found that patients experienced improvements in signs and symptoms of moderate-to-severe AD with upadacitinib regardless of prior response to dupilumab treatment [9]. Similar findings were observed in a Canadian multicenter retrospective study that evaluated the effectiveness of upadacitinib in adult patients with moderate-to-severe AD who had been previously treated with dupilumab [10].

To more fully characterize which patients are more likely to benefit from switching from dupilumab to abrocitinib, this analysis evaluated the efficacy of abrocitinib in patients with moderate-to-severe AD who were categorized as responders or nonresponders based on whether or not their disease signs and symptoms improved with dupilumab as measured by specific response criteria.

METHODS

Patients and Efficacy Assessments

Study design details of JADE DARE and JADE EXTEND (NCT03422822) were described previously [6, 8]. Briefly, JADE DARE [6] was a head-to-head, randomized, phase 3 clinical trial designed to compare the efficacy and safety of abrocitinib 200 mg once daily with dupilumab 300 mg every 2 weeks in patients receiving topical medicated therapy for 26 weeks. Patients from JADE DARE could enroll in the ongoing phase 3 long-term extension trial JADE EXTEND [8] to receive abrocitinib if they provided informed consent and had completed the full treatment course in JADE DARE. Study documents and procedures were approved by the appropriate institutional review boards/ethics committees at each study site. These trials were conducted in accordance with the ethical principles from the Declaration of Helsinki, International Ethical Guidelines for Biomedical Research Involving Human Subjects from the Council for International Organizations of Medical Sciences, and International Council for Harmonisation Good Clinical Practice Guidelines. Informed consent was obtained from all individual participants included in both trials.

This post hoc, planned interim analysis included data from patients aged ≥ 18 years who were treated with subcutaneous dupilumab 300 mg biweekly (600-mg loading dose at baseline) in the JADE DARE trial and switched to abrocitinib 200 mg when enrolled in JADE EXTEND (data cutoff date: September 25, 2021). To comprehensively assess which patients benefited from switching to abrocitinib in EXTEND, a set of response criteria based on Investigator's Global Assessment (IGA), Eczema Area and Severity Index (EASI), Peak Pruritus Numerical Rating Scale (PP-NRS; used with permission from Regeneron Pharmaceuticals, Inc., and Sanofi), and Dermatology Life Quality Index (DLQI) scores or responses were used as outlined in Table 1 to characterize response at Week 26 of JADE DARE. These criteria were defined post hoc and were used to evaluate efficacy at Week 12 of JADE EXTEND (i.e., 12 weeks after switching to abrocitinib) in patients who did (responders) and did not (nonresponders) fulfill each criterion after 26 weeks of dupilumab treatment in JADE DARE. Efficacy assessments at Week 12 of JADE EXTEND are also outlined in Table 1. EASI scores and percentage change from baseline in EASI and PP-NRS scores at Week 26 in JADE DARE were also compared with the corresponding scores and percentage changes at Week 12 in JADE EXTEND. Adverse events (AEs) were evaluated at Week 26 of JADE DARE and Week 12 of JADE EXTEND.

Table 1 Response criteria at Week 26 of JADE DARE and corresponding efficacy assessments at Week 12 of JADE EXTEND

Response criterion at Week 26 of JADE DARE	Efficacy assessment at Week 12 of JADE EXTEND
IGA score of 1 (almost clear disease), 2 (mild disease), 3 (moderate disease), or 4 (severe disease)	Change in IGA score
IGA 0/1 response[a]	Maintenance or attainment of IGA 0/1 response[a]
EASI score of 7–16	Attainment of EASI score < 7, EASI score of 0–2, EASI-75, and EASI-90
EASI score ≥ 16	Changes in individual EASI scores Attainment of EASI score < 16, EASI-75, and EASI-90
EASI-50	Maintenance or attainment of EASI-50 and EASI-75
EASI-75	Maintenance or attainment of EASI-75 and EASI-90
EASI-90	Maintenance or attainment of EASI-90 and EASI-100
PP-NRS score of 2–4	Attainment of PP-NRS 0/1
PP-NRS score of 4–7	Attainment of PP-NRS score < 4, PP-NRS4, and PP-NRS 0/1
PP-NRS score ≥ 7	Changes in individual PP-NRS scores Attainment of PP-NRS score < 7, PP-NRS4, and PP-NRS 0/1
PP-NRS4	Maintenance or attainment of PP-NRS4 and PP-NRS 0/1
PP-NRS 0/1	Maintenance or attainment of PP-NRS 0/1
DLQI score of 2–5	Attainment of DLQI 0/1
DLQI score of 11–20	Attainment of DLQI score < 11 and DLQI score of 0–5
DLQI score of 21	Attainment of DLQI score < 21, DLQI score < 11, and DLQI score of 0–5
DLQI 0/1	Maintenance or attainment of DLQI 0/1

DLQI Dermatology Life Quality Index, *DLQI 0/1*, DLQI score of 0 or 1, *EASI* Eczema Area and Severity Index, *EASI-50* ≥ 50% improvement from baseline in EASI, *EASI-75* ≥ 75% improvement from baseline in EASI, *EASI-90* ≥ 90% improvement from baseline in EASI, *IGA* Investigator's Global Assessment, *PP-NRS* Peak Pruritus Numerical Rating Scale (used with permission from Regeneron Pharmaceuticals, Inc., and Sanofi), *PP-NRS 0/1* PP-NRS score of 0 or 1, *PP-NRS4* ≥ 4-point improvement from baseline in PP-NRS

[a]IGA 0/1 response defined as IGA score of 0 (clear) or 1 (almost clear) and ≥ 2-point improvement from baseline

Statistical Analysis

The full analysis set comprised all randomized patients who received at least one dose of study medication. Baseline value was defined as that from the baseline visit of JADE DARE. Data were reported as observed, and no imputations were made for missing data. Confidence intervals for response rates were based on normal approximation or the Clopper-Pearson exact method when there were 0% or 100% responders. Safety analyses included AEs that occurred up to 28 days after the last dupilumab dose in JADE DARE. In JADE EXTEND, AEs were included if they occurred up to 28 days after the last abrocitinib dose in EXTEND or until

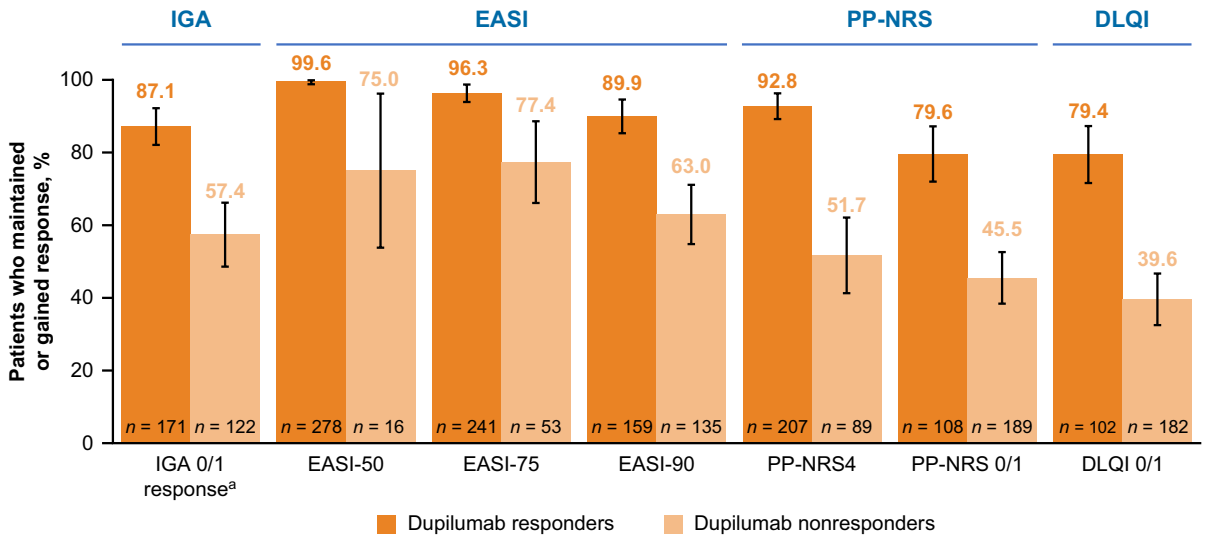


Fig. 1 Efficacy responses after 12-week switch to abrocitinib in dupilumab responders and nonresponders at Week 26 of JADE DARE. [a]IGA response defined as IGA score of 0 (clear) or 1 (almost clear) and ≥ 2-point improvement from baseline. *DLQI* Dermatology Life Quality Index, *DLQI 0/1* DLQI score of 0 or 1, *EASI* Eczema Area and Severity Index, *EASI-50* ≥ 50% improvement from baseline in EASI, *EASI-75* ≥ 75% improvement from baseline in EASI, *EASI-90* ≥ 90% improvement from baseline in EASI, *IGA* Investigator's Global Assessment, *PP-NRS* Peak Pruritus Numerical Rating Scale, *PP-NRS4* ≥ 4-point improvement from baseline in PP-NRS, *PP-NRS 0/1* PP-NRS score of 0 or 1

September 25, 2021 (data cutoff), whichever was earlier. Serious AEs were classified according to the investigator's assessment.

RESULTS

Patient Demographics and Baseline Disease Characteristics

Of 365 dupilumab-treated patients in JADE DARE, 316 were enrolled in the long-term extension trial JADE EXTEND; of these, 312 received abrocitinib 200 mg. Baseline demographics were largely comparable between dupilumab responders and nonresponders across the IGA score of 0 (clear) or 1 (almost clear) and ≥ 2-point improvement from baseline, ≥ 75% improvement from baseline in EASI (EASI-75), and ≥ 4-point improvement from baseline in PP-NRS (PP-NRS4) subgroups. Severe AD (i.e., IGA = 4) was more frequent in dupilumab IGA 0/1 and EASI-75 nonresponders than in responders (Table S1).

At Week 26 of JADE DARE, the number of dupilumab responders ranged from 121 to 316, depending on the evaluated response criterion; the number of nonresponders ranged from 21 to 220. Of those, 113 to 292 responders and 17 to 197 nonresponders switched to abrocitinib 200 mg in JADE EXTEND (Table S2).

Efficacy Responses 12 Weeks After Switching to Abrocitinib

Most of the Week 26 JADE DARE dupilumab responders maintained their response in IGA 0/1 (87.1%), ≥ 50% improvement from baseline in EASI (EASI-50; 99.6%), EASI-75 (96.3%), ≥ 90% improvement from baseline in EASI (EASI-90; 89.9%), PP-NRS4 (92.8%), PP-NRS score of 0 or 1 (PP-NRS 0/1; 79.6%), and DLQI score of 0 or 1 (DLQI 0/1; 79.4%) at Week 12 after switching to abrocitinib 200 mg (Fig. 1). Of the Week 26 JADE DARE dupilumab nonresponders, up to 77.4% gained response in IGA 0/1 (57.4%), EASI-50 (75.0%), EASI-75 (77.4%), EASI-90 (63.0%),

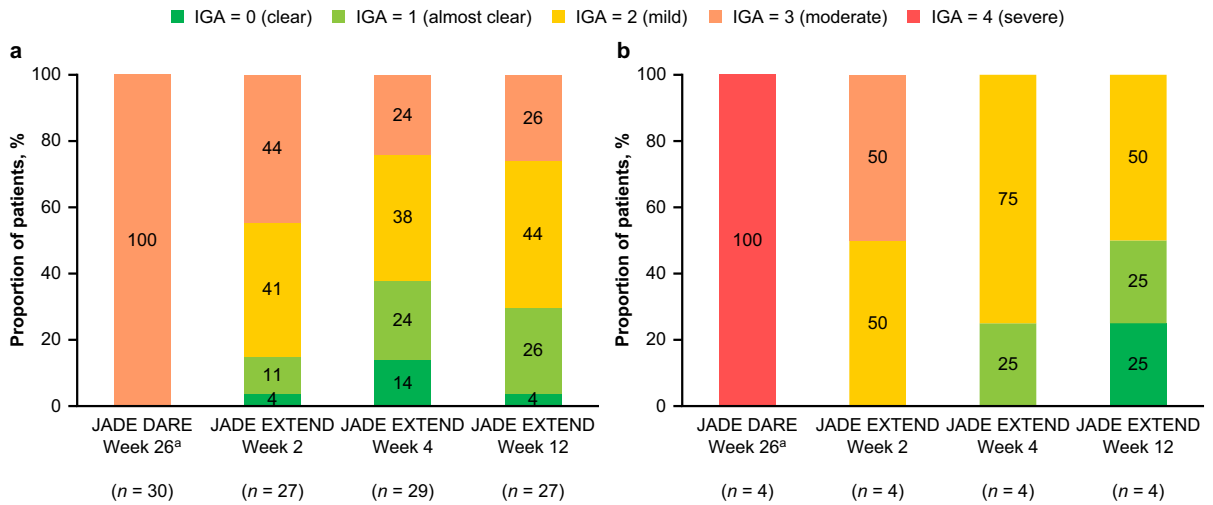


Fig. 2 Proportions of dupilumab-treated patients with **a** IGA = 3 and **b** IGA = 4 at Week 26 of JADE DARE in each IGA category by JADE EXTEND visit after switch to abrocitinib. [a]At the time of the switch. *IGA* Investigator's Global Assessment

PP-NRS4 (51.7%), PP-NRS 0/1 (45.5%), and DLQI 0/1 (39.6%) at Week 12 after switching to abrocitinib 200 mg (Fig. 1).

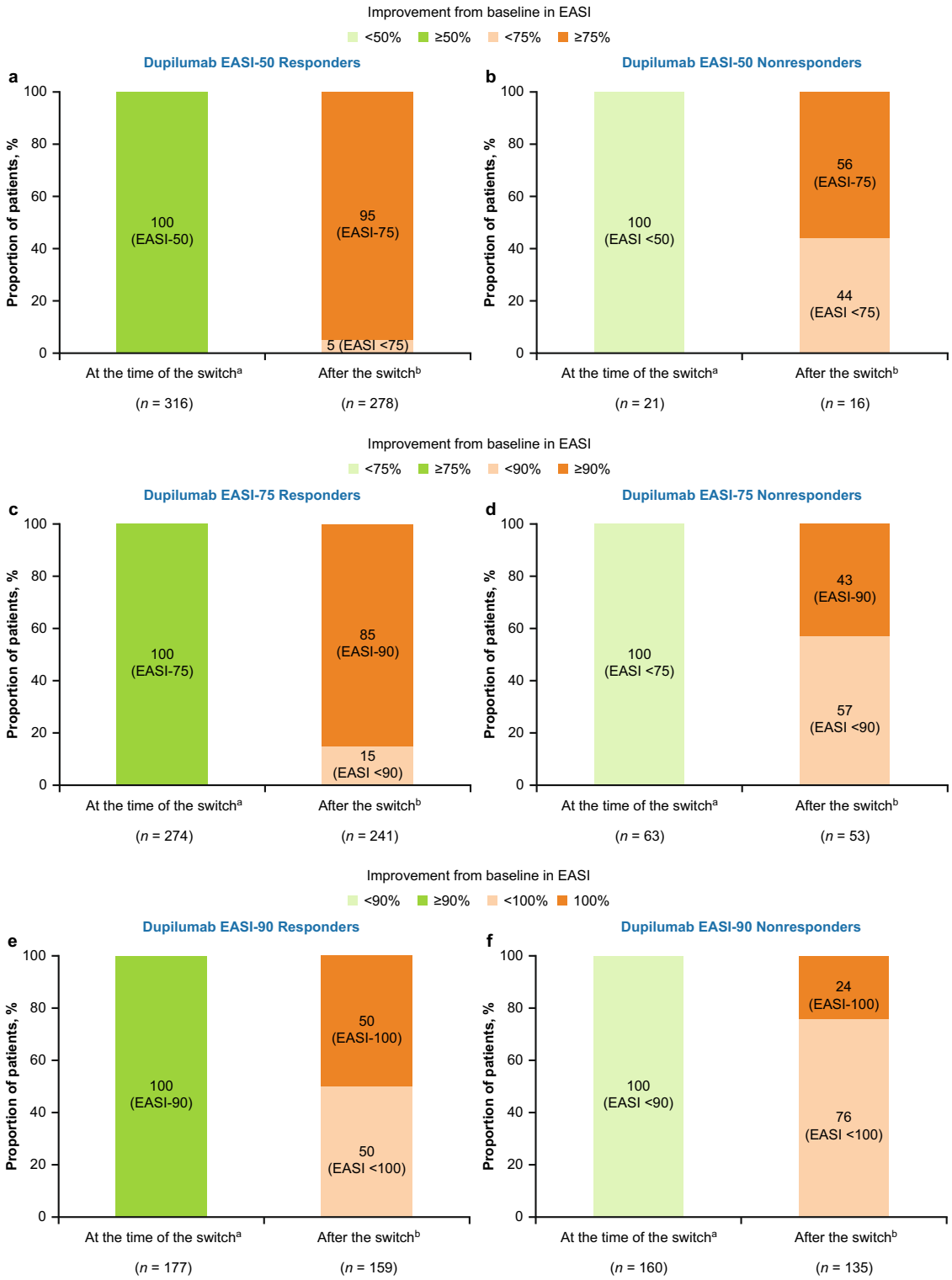
IGA Score Change by Visit After Switching to Abrocitinib

Most patients with an IGA score of 3 or 4 after 26 weeks of dupilumab treatment gained an improvement in IGA score (i.e., IGA < 3) as early as Week 2 after switching to abrocitinib. None of these patients had an IGA 4 (severe disease) at Week 12 after switching to abrocitinib (Fig. 2). Patients who achieved an IGA score of 1 or 2 after 26 weeks of dupilumab treatment also gained an improvement in IGA score after switching to abrocitinib. Of the dupilumab-treated patients with an IGA score of 2 at Week 26 of JADE DARE, 29% (26/91) achieved an IGA score of 0 (clear) and 37% (34/91) achieved an IGA score of 1 (almost clear) after switching to abrocitinib. Of the dupilumab-treated patients with an IGA score of 1 at Week 26 of JADE DARE, 40% (51/126) achieved an IGA score of 0 after the switch.

EASI Response 12 Weeks After Switching to Abrocitinib

Patients gained improvements in EASI after switching to abrocitinib; 91% (10/11) of dupilumab-treated patients who had an EASI score ≥ 16 at Week 26 of JADE DARE achieved an EASI score < 16 and experienced improvements from baseline in individual EASI scores after switching to abrocitinib (Video 1). A substantial proportion of these patients with an EASI score ≥ 16 at Week 26 of JADE DARE gained improvements in EASI and achieved EASI-75 (64% [7/11]) and EASI-90 (36% [4/11]) at Week 12 after switching to abrocitinib.

Of the dupilumab-treated patients with an EASI score of 7–16 at Week 26 of JADE DARE, 78% (28/36) had an EASI score of < 7 at Week 12 after switching to abrocitinib. Considerable proportions of these patients with an EASI score of 7–16 at Week 26 of JADE DARE gained improvements in EASI and achieved EASI-75 (81% [29/36]), EASI-90 (56% [20/36]), and an EASI score of 0–2 (47% [17/36]) at Week 12 after switching to abrocitinib.


Improvement from baseline in EASI
<50%
≥50%
<75%
≥75%
a
Dupilumab EASI-50 Responders
Proportion of patients, %
100
(EASI-50)
95
(EASI-75)
5 (EASI <75)
At the time of the switch[a]
(n = 316)
After the switch[b]
(n = 278)
b
Dupilumab EASI-50 Nonresponders
100
(EASI <50)
56
(EASI-75)
44
(EASI <75)
At the time of the switch[a]
(n = 21)
After the switch[b]
(n = 16)
Improvement from baseline in EASI
<75%
≥75%
<90%
≥90%
c
Dupilumab EASI-75 Responders
100
(EASI-75)
85
(EASI-90)
15
(EASI <90)
At the time of the switch[a]
(n = 274)
After the switch[b]
(n = 241)
d
Dupilumab EASI-75 Nonresponders
100
(EASI <75)
43
(EASI-90)
57
(EASI <90)
At the time of the switch[a]
(n = 63)
After the switch[b]
(n = 53)
Improvement from baseline in EASI
<90%
≥90%
<100%
100%
e
Dupilumab EASI-90 Responders
100
(EASI-90)
50
(EASI-100)
50
(EASI <100)
At the time of the switch[a]
(n = 177)
After the switch[b]
(n = 159)
f
Dupilumab EASI-90 Nonresponders
100
(EASI <90)
24
(EASI-100)
76
(EASI <100)
At the time of the switch[a]
(n = 160)
After the switch[b]
(n = 135)

◂**Fig. 3** Proportions of dupilumab-treated patients who were **a** EASI-50 responders, **b** EASI-50 nonresponders, **c** EASI-75 responders, **d** EASI-75 nonresponders, **e** EASI-90 responders, and **f** EASI-90 nonresponders at Week 26 of JADE DARE and gained incremental responses at Week 12 after switching to abrocitinib. [a]JADE DARE Week 26. [b]JADE EXTEND Week 12. *EASI* Eczema Area and Severity Index, *EASI-50* ≥ 50% improvement from baseline in EASI, *EASI* < *50* < 50% improvement from baseline in EASI, *EASI-75* ≥ 75% improvement from baseline in EASI, *EASI* < *75* < 75% improvement from baseline in EASI, *EASI-90* ≥ 90% improvement from baseline in EASI, *EASI* < *90* < 90% improvement from baseline in EASI, *EASI-100* 100% improvement from baseline in EASI, *EASI* < *100* < 100% improvement from baseline in EASI

Gain of Response After Switching to Abrocitinib

Of the dupilumab-treated patients who were EASI-50 responders and EASI-50 nonresponders at Week 26 of JADE DARE, 95% (264/278) and 56% (9/16), respectively, gained response and achieved EASI-75 at Week 12 after switching to abrocitinib (Fig. 3). Of the dupilumab EASI-75 responders and EASI-75 nonresponders at Week 26 of JADE DARE, 85% (205/241) and 43% (23/53), respectively, gained response and achieved EASI-90 at Week 12 after switching (Fig. 3). Furthermore, of those who were dupilumab EASI-90 responders and EASI-90 nonresponders at Week 26 of JADE DARE, 50% (80/159) and 24% (33/135), respectively, gained response and achieved EASI-100 after switching to abrocitinib (Fig. 3).

PP-NRS Response 12 Weeks After Switching to Abrocitinib

Patients gained improvements in PP-NRS after switching to abrocitinib; 75% (12/16) of dupilumab-treated patients who had a PP-NRS score ≥ 7 at JADE DARE Week 26 achieved a PP-NRS score < 7 and experienced improvements from baseline in individual PP-NRS scores after switching to abrocitinib (Video 1). A considerable proportion of these patients with a PP-NRS score ≥ 7 at JADE DARE Week 26 gained improvements in PP-NRS and achieved PP-NRS4 (62% [10/16]) and PP-NRS 0/1 (19% [3/16]) at Week 12 after switching to abrocitinib.

Of the dupilumab-treated patients with a PP-NRS score of 4–7 at Week 26 of JADE DARE, 57% (43/75) had a PP-NRS score < 4 at Week 12 after switching to abrocitinib. Considerable proportions of these patients with a PP-NRS score of 4–7 at Week 26 of JADE DARE gained improvements in PP-NRS and achieved PP-NRS4 (64% [48/75]) and PP-NRS 0/1 (29% [22/75]) at Week 12 after switching to abrocitinib.

Among the dupilumab-treated patients who had a PP-NRS score of 2–4 at Week 26 in JADE DARE, 55% (72/132) gained response and achieved PP-NRS 0/1 after switching to abrocitinib. After the switch, PP-NRS 0/1 response was gained by 71% (146/207) of dupilumab-treated patients who were PP-NRS4 responders at Week 26 of JADE DARE and 29% (26/90) who were PP-NRS4 nonresponders.

DLQI Response 12 Weeks After Switching to Dupilumab

Of the dupilumab-treated patients with a DLQI score of 21 at JADE DARE Week 26, 100% (2/2) had a DLQI score < 21, 100% (2/2) had a DLQI score < 11, and 50% (1/2) had a DLQI score of 0–5 at Week 12 after switching to abrocitinib. A substantial proportion of patients with a DLQI score of 11–20 at Week 26 of JADE DARE gained response and achieved a DLQI score < 11 (65% [11/17]) and a DLQI score of 0–5 (41% [7/17]) at Week 12 after switching to abrocitinib. Of the dupilumab-treated patients with a DLQI score of 2–5 at Week 26 of JADE DARE, 50% (54/109) gained response and achieved DLQI 0/1 at Week 12 after switching to abrocitinib.

EASI Scores and PP-NRS Scores at Week 26 of JADE DARE and Week 12 of JADE EXTEND

EASI scores were lower with abrocitinib at Week 12 of JADE EXTEND (median [IQR], 0.6 [0.0–2.0]) than with dupilumab at Week 26 of JADE DARE (median [IQR], 2.2 [0.6–5.4]). Percentage change from baseline in EASI score was

Table 2 Adverse events during JADE DARE and up to Week 12 of JADE EXTEND in all dupilumab-treated patients from JADE DARE who were enrolled in JADE EXTEND

n (%)	**Dupilumab 300 mg Q2W[a] *n* = 316**	**Abrocitinib 200 mg QD[b] *n* = 312**
Patients with AEs	205 (65)	178 (57)
Patients with serious AEs	2 (1)	9 (3)
Patients with severe AEs	5 (2)	7 (2)
Patients who discontinued from the study because of AEs	0	14 (4)
Most frequently reported AEs (≥ 5%)		
Nausea	6 (2)	50 (16)
Conjunctivitis	32 (10)	1 (0.3)
Acne	9 (3)	27 (9)
Headache	21 (7)	21 (7)

Patients were counted only once per treatment in each row

AE adverse event, *Q2W* every 2 weeks, *QD* once daily

[a]Dupilumab safety profile evaluated during JADE DARE. Data were included up to 28 days after the last dupilumab dose

[b]Abrocitinib safety profile evaluated during JADE EXTEND, up to Week 12. Data were included up to 28 days after either the last abrocitinib dose or until the data cutoff date, whichever was earlier

greater after switching to abrocitinib (median [IQR], −97.8 [−100.0 to −90.9] at Week 12 in JADE EXTEND) than with dupilumab (median [IQR], −91.4 [−97.3 to −79.9] at Week 26 in JADE DARE). Similarly, percentage change from baseline in PP-NRS was greater with abrocitinib at Week 12 of JADE EXTEND (median [IQR], −85.7 [−100.0 to −57.1]) than with dupilumab at Week 26 of JADE DARE (median [IQR], −71.4 [−85.7 to −44.4]).

Safety Summary in Dupilumab-Treated Patients from JADE DARE Who Were Enrolled in JADE EXTEND

More patients reported AEs with dupilumab during 26 weeks of treatment in JADE DARE (65%) than with abrocitinib 200 mg up to 12 weeks of JADE EXTEND (57%; Table 2). Serious AEs were reported in nine patients (3%) treated with abrocitinib 200 mg in JADE EXTEND, each occurring once: thrombocytopenic purpura, appendicitis, *Borrelia* infection, vulvovaginal candidiasis, foot fracture, intervertebral disc protrusion, spontaneous abortion, renal failure, and drug eruption. Serious AEs of asthma and atopic dermatitis occurred in two patients (1%) who received dupilumab in JADE DARE, each occurring once. Severe AEs were reported in seven (2%) patients treated with abrocitinib 200 mg in JADE EXTEND, each occurring once: eye pain, chills, appendicitis, *Borrelia* infection, COVID-19 infection, blood creatine phosphokinase increase, myalgia, headache, pregnancy, ovarian cyst rupture, and drug eruption. Severe AEs occurred in five (2%) patients treated with dupilumab in JADE DARE, each occurring once: toothache, milk allergy, alanine aminotransferase increase, sleep disorder, asthma, and pruritus; patients could report two or more different severe AEs. There were no discontinuations due to AEs with dupilumab in JADE DARE; of the 312 patients who switched to abrocitinib 200 mg, 14 (4%) discontinued the study because of AEs within the first 12 weeks of JADE EXTEND (Table 2).

The most frequent AEs with dupilumab in JADE DARE and abrocitinib 200 mg in JADE EXTEND were nausea (2%, 16%), conjunctivitis (10%, 0.3%), acne (3%, 9%), and headache (7%, 7%) (Table 2). Conjunctivitis occurred in 32 (10%) dupilumab-treated patients from JADE DARE who were enrolled in JADE EXTEND. One (0.3%) patient had conjunctivitis after switching to abrocitinib 200 mg in JADE EXTEND.

DISCUSSION

This post hoc analysis evaluated the efficacy of abrocitinib in dupilumab-treated patients in JADE DARE who switched to abrocitinib in JADE EXTEND. While nearly all patients (up to 99.6%) who responded to dupilumab treatment in JADE DARE maintained their response 12 weeks after switching to abrocitinib in JADE EXTEND, a substantial proportion of those (up to 77.4%) who had insufficient/inadequate response to dupilumab gained response after switching to abrocitinib. Notably, dupilumab-treated patients with residual itch after 26 weeks in JADE DARE gained response after switching to abrocitinib and achieved an itch-free state (PP-NRS 0/1). Similarly, a substantial proportion of dupilumab-treated patients who had mild-to-severe AD (based on IGA score) after 26 weeks in JADE DARE gained response and had clear or almost clear skin after switching to abrocitinib. These findings are particularly relevant given that a recent post hoc analysis of data from phase 2b and phase 3 trials JADE MONO-1 and JADE MONO-2 showed that patients who achieved higher threshold efficacy end points with abrocitinib were more likely to report that their AD had no effect on their quality of life [11]. Together, these results suggest that in patients whose signs and symptoms of AD improve with dupilumab treatment, switching to abrocitinib can yield further improvements, potentially reaching a disease-free state. These findings are consistent with other post hoc analyses of the JADE clinical trials, which showed that response to previous treatment with systemic therapies, including dupilumab, had no impact on the response to subsequent treatment with abrocitinib [7, 8]. Moreover, the current post hoc analysis further characterizes the patient population with AD who had an inadequate response to dupilumab using broader criteria for defining nonresponse that includes EASI score ≥ 16, PP-NRS score ≥ 7, and IGA score of 3 or 4. However, the small sample size of the subgroups with moderate or severe IGA, EASI score of 7–16, EASI ≥ 16, PP-NRS score of 4–7, PP-NRS ≥ 7, DLQI score of 11–20, or DLQI score of 21 at Week 26 of JADE DARE may limit interpretation of results.

While substantial proportions of patients gained response after switching to abrocitinib, those who initially responded to dupilumab treatment were more likely to gain further improvements in AD signs and symptoms than those who had insufficient/inadequate response to dupilumab. These findings are consistent with other studies in patients with AD or other chronic inflammatory conditions, which showed that those who did not respond to previous biologic treatments were more likely to have a reduced response to subsequent treatments [8, 12, 13].

The safety profile of abrocitinib after switching from dupilumab was consistent with that of previous safety analyses [6, 8, 14]. Serious AEs were relatively rare; occurrence of conjunctivitis was less frequent with abrocitinib in JADE EXTEND compared with dupilumab in JADE DARE, while nausea and acne were more frequent with abrocitinib in JADE EXTEND than with dupilumab in JADE DARE. The most frequent AEs observed with abrocitinib in the current analysis are similar to those seen during 26 weeks of treatment in JADE DARE [6] and in an integrated safety analysis of abrocitinib in 12- to 16-week studies from the JADE clinical trial program [15]. Long-term safety of abrocitinib was not evaluated in this post hoc analysis but is an important consideration during the shared decision-making process between patients and their physicians. Results from an integrated safety analysis of abrocitinib showed that the safety profile of abrocitinib is suitable for long-term use, provided that the dose and patient are appropriately selected [15]. Appropriate patient selection based on age, cardiovascular risk factors, and individual characteristics may minimize potential risks associated with JAK

inhibitors [15, 16]. These risks may be further reduced by targeting the minimal effective dose and a flexible-dosing treatment strategy for appropriate patients [15, 16].

One limitation of the current study is that the study designs for JADE DARE and JADE EXTEND differed regarding concomitant topical therapy. In JADE DARE, participants were required to apply topical therapy, while it was optional in JADE EXTEND [6, 8]. This study may also be limited by the small number of participants in the subgroups that were included in the analysis. Additionally, the study duration was short, with an exposure time for dupilumab of 26 weeks in JADE DARE, but only 12 weeks for abrocitinib in JADE EXTEND, which led to an imbalance in the safety data and did not allow an evaluation of the longer-term safety of abrocitinib.

CONCLUSION

In conclusion, this post hoc analysis suggests that switching to abrocitinib 200 mg may be an effective alternative with a favorable safety profile for patients with moderate-to-severe AD who did not achieve optimal outcomes or are experiencing conjunctivitis with dupilumab.

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Declarations

Conflict of Interest. **Jonathan I. Silverberg** served as an investigator for Celgene, Eli Lilly and Company, F. Hoffmann-La Roche, Menlo Therapeutics, Realm Therapeutics, Regeneron Pharmaceuticals, and Sanofi Genzyme; as a consultant for Pfizer Inc., AbbVie, Anacor, AnaptysBio, Arena Pharmaceuticals, Dermavant, Dermira, Eli Lilly and Company, Galderma, GlaxoSmithKline, Glenmark, Incyte, Kiniksa Pharmaceuticals, LEO Pharma, Menlo

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