Abrocitinib induction, randomized withdrawal, and retreatment in patients with moderate-to-severe atopic dermatitis: Results from the JAK1 Atopic Dermatitis Efficacy and Safety (JADE) REGIMEN phase 3 trial

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Background: The heterogeneous course of moderate-to-severe atopic dermatitis necessitates treatment flexibility.

Objective: We evaluated the maintenance of abrocitinib-induced response with continuous abrocitinib treatment, dose reduction or withdrawal, and response to treatment reintroduction following flare (JAK1 Atopic Dermatitis Efficacy and Safety [JADE] REGIMEN: National Clinical Trial 03627767).

Methods: Patients with moderate-to-severe atopic dermatitis responding to open-label abrocitinib 200 mg monotherapy for 12 weeks were randomly assigned in a 1:1:1 ratio to blinded abrocitinib (200 or 100 mg) or placebo for 40 weeks. Patients experiencing flare received rescue treatment (abrocitinib 200 mg plus topical therapy).

Results: Of 1233 patients, 798 responders to induction (64.7%) were randomly assigned. The flare probability during maintenance was 18.9%, 42.6%, and 80.9% with abrocitinib 200 mg, abrocitinib 100 mg, and placebo, respectively. Among patients with flare in the abrocitinib 200 mg, abrocitinib 100 mg, and placebo groups, 36.6%, 58.8%, and 81.6% regained investigator global assessment 0/1 response, respectively, and 55.0%, 74.5%, and 91.8% regained eczema area and severity index response, respectively, with rescue treatment. During maintenance, 63.2% and 54.0% of patients receiving abrocitinib 200 and 100 mg, respectively, experienced adverse events.

Limitations: The definition of protocol-defined flare was not established, limiting the generalizability of findings.

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Conclusion: Induction treatment with abrocitinib was effective; most responders continuing abrocitinib did not flare. Rescue treatment with abrocitinib plus topical therapy effectively recaptured response. (J Am Acad Dermatol 2022;86:104-12.)

Key words: abrocitinib; atopic dermatitis; JADE REGIMEN; JAK1 inhibitor; response; treatment.

INTRODUCTION

Atopic dermatitis (AD) is a chronic, relapsing/remitting, inflammatory skin disease characterized by pruritus and eczematous lesions.[1] The heterogeneous disease course of moderate-to-severe AD, treatment interruption due to poor adherence, or changes in disease factors require dosing flexibility.[2] However, there is limited evidence to guide intermittent/flexible dosing regimens in this population.

Abrocitinib is a Janus kinase 1 selective inhibitor under investigation for the treatment of moderate-to-severe AD with inadequate response to topical therapy. Janus kinase 1 inhibition modulates multiple downstream signaling pathways critical to the pathogenesis of AD, including interleukin (IL) 4, IL-13, IL-22, IL-31, and thymic stromal lymphopoietin.[3-5] In phase 3 studies (JAK1 Atopic Dermatitis Efficacy and Safety [JADE] MONO-1: NCT03349060; JADE MONO-2: NCT03575871), significantly greater proportions of adolescents and adults receiving abrocitinib monotherapy (200 mg or 100 mg) achieved investigator global assessment (IGA) responses of clear (0) or almost clear (1) with ≥2-grade improvement, ≥75% improvement in eczema area and severity index (EASI-75) responses, and ≥4-point improvements from baseline in peak pruritus numerical rating scale (PP-NRS, Regeneron Pharmaceuticals, Inc. and Sanofi [2017]) responses compared with placebo, with a manageable and consistent safety profile.[6,7] Abrocitinib combined with medicated topical therapy was similarly well tolerated and effective at controlling moderate-to-severe AD in adolescents (JADE TEEN: NCT03796676) and adults (JADE COMPARE: NCT03720470).[8-10]

The effects of abrocitinib are mediated through reversible and selective inhibition of Janus kinase 1, suggesting that continuous treatment might be necessary to sustain response. However, the benefit-to-risk profile of a flexible/intermittent dosing regimen remains an open question. To evaluate the feasibility of a flexible treatment paradigm in this patient population, we conducted JADE REGIMEN (NCT03627767), a phase 3 induction-randomized withdrawal trial of abrocitinib. The trial was designed to assess the following: (1) the maintenance of clinical responses following an initial response to 12 weeks of open-label abrocitinib 200 mg; and (2) the ability to recapture responses with abrocitinib 200 mg combined with medicated topical therapy following flares.

CAPSULE SUMMARY

- The chronic, heterogeneous nature of moderate-to-severe atopic dermatitis necessitates flexible treatment regimens to optimize benefit-to-risk ratio.
- JAK1 Atopic Dermatitis Efficacy and Safety REGIMEN demonstrates that most patients with moderate-to-severe atopic dermatitis who initially respond to abrocitinib maintain response with reduced dosing.
- Additionally, abrocitinib plus topical therapy effectively recaptures response after flaring.

METHODS

Patients

Eligible patients were 12 years of age or older with a body weight of 40 kg or greater, a confirmed diagnosis of AD per Hanifin and Rajka's[11] diagnostic criteria, and moderate-to-severe AD (IGA ≥ 3; EASI[12] ≥16; affected percentage of body surface area ≥ 10; and PP-NRS ≥ 4[13]) at baseline. In addition, patients had a documented history (≤6 months before screening) of inadequate response to treatment with ≥4 consecutive weeks of medicated topical therapy or previous systemic therapy for AD.

Patients with psychiatric conditions (details are provided in Supplemental Methods, Section B; available via Mendeley at https://data.mendeley.com/datasets/xjn2xnpk2h/1) or with medical history of conditions associated with thrombocytopenia, coagulopathy, or platelet dysfunction were excluded. Patients were required to wash out prior AD treatments (eg, biologic therapies, including dupilumab) before study initiation. Prior dupilumab use was not an exclusion criterion. Oral antihistamines and topical nonmedicated emollients were permitted throughout the study.

Study design

JADE REGIMEN was a multicenter, responder-enriched, double-blinded, placebo-controlled, phase

Abbreviations used:

AD:	atopic dermatitis
AE:	adverse event
EASI:	eczema area and severity index
IGA:	investigator global assessment
IL:	interleukin
IR:	incidence rate
PP-NRS:	peak pruritus numerical rating scale
TEAE:	treatment-emergent adverse event

3 randomized withdrawal study with rescue treatment in flaring patients that was conducted between June 11, 2018, and October 7, 2020, in Argentina, Belgium, Brazil, Bulgaria, Canada, Chile, China, Germany, Israel, Italy, Latvia, Mexico, Netherlands, Poland, Romania, Russian Federation, Serbia, Slovakia, Spain, Taiwan, and the United States.

Patients initiated treatment within 28 days of the screening visit. The study consisted of 3 periods (Supplemental Fig 1 available via Mendeley at https://data.mendeley.com/datasets/xjn2xnpk2h/1.) The first was a 12-week, open-label induction period to determine response to once-daily abrocitinib 200 mg monotherapy. In the second period, induction period responders (defined as patients who achieved IGA 0/1 response [with ≥2-grade improvement] and EASI-75 response) entered a 40-week, double-blinded, randomized maintenance-withdrawal period in which responders were randomly assigned in 1:1:1 ratio via an interactive voice response system to receive once-daily monotherapy with abrocitinib 200 mg, abrocitinib 100 mg, or placebo. Randomization was stratified by age (<18 years of age and ≥18 years).

In the third period, patients who experienced a flare (loss of response) requiring rescue, defined as ≥50% loss of initial EASI response at week 12 with a new IGA score ≥2 during the maintenance period, entered a 12-week open-label rescue period of abrocitinib 200 mg with medicated topical therapy. Topical therapy options were corticosteroids, calcineurin inhibitors, and crisaborole, used per investigator's usual practice. Treatment could be interrupted by the investigator for safety concerns or observation of abnormal laboratory tests for ≤28 consecutive days. Patients who did not meet the responder criteria at the end of the open-label induction period had the option to enter a long-term extension safety study. Alternatively, they could discontinue treatment and enter a 4-week follow-up period.

The study was conducted in compliance with the ethical principles from the Declaration of Helsinki using International Council for Harmonization Good Clinical Practice Guidelines. All local regulatory requirements were followed. This research was approved by institutional review boards or ethics committees at each site. Internal and external review committees monitored the safety of patients throughout the study. All patients provided written informed consent.

Outcome measures

The primary endpoint was the loss of response requiring rescue medication during the maintenance period. The key secondary endpoint was loss of IGA 0/1 response during the maintenance period. Additional efficacy assessments included the proportion of patients who achieved IGA 0/1 response; ≥50%, ≥75%, ≥90%, and 100% EASI improvements; ≥4-point improvement in PP-NRS (PP-NRS-4 response); and change from baseline in SCORing atopic dermatitis subjective assessment of itch and sleep loss[14] at all scheduled timepoints. The same efficacy endpoints were assessed throughout the rescue period.

Additional patient-reported outcomes included the change from baseline at all scheduled time points in patient global assessment, dermatology life quality index,[15] children's dermatology life quality index,[16] patient-oriented eczema measure,[17] and pruritus and symptoms assessment in atopic dermatitis.[18] Incidence of adverse events (AEs), serious AEs, AEs leading to discontinuation, and laboratory abnormalities were recorded.

Statistical analysis

For the randomized maintenance-withdrawal period, enrollment of 600 patients (200 each in the abrocitinib 200 mg, abrocitinib 100 mg, and placebo arms) were considered necessary to provide 94% power to detect a ratio of median time to flare of ≥1.5 times between abrocitinib (200 or 100 mg) and placebo. Based on prior data, it was assumed that at least 44% of patients would meet the protocol-defined criteria for response at week 12 of the open-label induction period, hence requiring approximately 1370 patients to be enrolled in that induction period.

The family-wise type I error rate for testing the primary and key secondary endpoints was strictly controlled at 5% using a sequential, gatekeeping procedure (Supplemental Fig 2 available via Mendeley at https://data.mendeley.com/datasets/xjn2xnpk2h/1.) Binary data were analyzed using the Cochran-Mantel-Haenszel test, adjusted by randomization strata and disease severity at study baseline (moderate [IGA = 3] or severe [IGA = 4]), and normal approximation. Continuous data were

analyzed using a mixed-effect model with repeated measures. The model included factors for visit, treatment group, treatment-by-visit interaction, randomization stratification, and disease severity at study baseline. Missing responses for patients who permanently discontinued the study were defined as nonresponders at all visits after discontinuation.

The analysis population for efficacy endpoints was the full analysis set, defined as all patients randomly assigned to treatment who received at least 1 dose of study medication (Supplemental Fig 3 available via Mendeley at https://data.mendeley.com/datasets/xjn2xnpk2h/1.) Safety was assessed in the safety analysis set, defined as all patients who received at least 1 dose of study medication. There were the full analysis set and the safety analysis set populations for each phase of the study, but this report was focused on the randomized period. Because of the study design, planned cumulative dosing was different between arms. To account for differences in exposure between arms, comparisons were based on incidence rates (IR) and were evaluated as follows: (Number of patients with event/Exposure of patients free of event or until they have event). IRs were reported as patients with events per 100 patient years. Safety was also analyzed using descriptive statistics.

RESULTS

Patients

Overall, 1233 patients were treated in the open-label induction, 798 were randomly assigned to the blinded period, and 351 required rescue because of a protocol-defined flare (Supplemental Fig 3). The median (interquartile range) age of the patient population was 28.0 (20.0-41.0) years. White (75.5%), Asian (15.9%), and Black (6.1%) patients were included. Based on IGA score, 59.1% and 40.9% of patients had moderate and severe disease, respectively (Table I).

Efficacy

Open-label induction period. After 12 weeks of open-label induction with abrocitinib 200 mg monotherapy, a total of 798 (64.7%) patients met the protocol-defined response (IGA 0/1 and EASI-75) and were randomly assigned into the maintenance period (Supplemental Fig 3). At the end of the induction period, 65.9% (95% CI, 63.3-68.6), 75.6% (95% CI, 73.1-78.0), and 68.3% (95% CI, 65.3-71.3) of patients achieved IGA 0/1, EASI-75, and PP-NRS responses, respectively (Supplemental Fig 4 available via Mendeley at https://data.mendeley.com/datasets/xjn2xnpk2h/1.)

Maintenance period. Induction responders were randomly assigned to receive 200 mg of abrocitinib (n = 266), 100 mg of abrocitinib (n = 265), or placebo (n = 267). During this period, 44 (16.5%) of 266 in the abrocitinib 200 mg group, 105 (39.6%) of 265 in the abrocitinib 100 mg group, and 207 (77.5%) of 267 patients in the placebo group had a protocol-defined flare (defined as ≥50% loss of initial EASI response at week 12 with a new IGA score of ≥2).

At the end of maintenance, the cumulative probability of experiencing a flare was 18.9% (95% CI, 14.2-24.9), 42.6% (95% CI, 36.3-49.5), and 80.9% (95% CI, 75.8-85.6) in the abrocitinib 200 mg, abrocitinib 100 mg, and placebo groups, respectively. The respective Kaplan-Meier estimate of median time to protocol-defined flare was 28 days (95% CI, 28-29) in the placebo arm and was not reached in either abrocitinib arm (Fig 1, *A*).

Risk of flare was significantly reduced with abrocitinib 200 mg versus placebo (hazard ratio, 0.10; 95% CI, 0.070-0.136; $P < .0001$), abrocitinib 100 mg versus placebo (hazard ratio, 0.27; 95% CI, 0.211-0.341; $P < .0001$), and abrocitinib 200 mg versus abrocitinib 100 mg (hazard ratio, 0.36; 95% CI, 0.255-0.516; $P < .0001$).

A similar pattern of statistical significance was seen with the more-stringent definition of loss of IGA 0/1 response (key secondary endpoint; Fig 1, *B*). A higher proportion of patients receiving either dose of abrocitinib maintained IGA 0/1, EASI-75, EASI-90, and PP-NRS-4 responses compared with placebo at study weeks 16 (4 weeks after randomization), 28, 40, and 52, respectively (Supplemental Table I available via Mendeley at https://data.mendeley.com/datasets/xjn2xnpk2h/1.)

Patients receiving abrocitinib at 200 or 100 mg maintenance who did not flare maintained a median EASI of 0.6 throughout or 0.8-1.6, respectively, which was similar to the median EASI at the end of induction (Supplemental Fig 5 available via Mendeley at https://data.mendeley.com/datasets/xjn2xnpk2h/1.) Similarly, median PP-NRS was also maintained in the abrocitinib 200 mg and 100 mg arms (Supplemental Fig 6 available via Mendeley at https://data.mendeley.com/datasets/xjn2xnpk2h/1.)

Rescue period. Overall, 351 patients, including 43 (16.2%), 104 (39.2%), and 204 (76.4%) from the abrocitinib 200 mg, abrocitinib 100 mg, and placebo maintenance arms, respectively, entered the rescue period. At week 12 of rescue with abrocitinib 200 mg and prescription topical corticosteroids, the EASI-75 response recapture rates were 55.0%, 74.5%, and 91.8% in the abrocitinib 200 mg,

Table I. Demographics, baseline disease, and treatment characteristics of study patients

		Randomized maintenance period				
	Open-label induction period	All	Placebo	Abrocitinib 100 mg	Abrocitinib 200 mg	Rescue period
Characteristic	**n = 1233**	**n = 798**	**n = 267**	**n = 265**	**n = 266**	**n = 351**
Age, y						
<18	246 (20.0)	145 (18.2)	49 (18.4)	49 (18.5)	47 (17.7)	64 (18.2)
Median (Q1, Q3)	28.0 (20.0, 41.0)	29.0 (20.0, 41.0)	29.0 (20.0, 40.0)	29.0 (20.0, 41.0)	28.0 (20.0, 42.0)	30.0 (21.0, 41.0)
Men, n (%)	684 (55.5)	439 (55.0)	141 (52.8)	148 (55.8)	150 (56.4)	198 (56.4)
Race, n (%)						
White	931 (75.5)	621 (77.8)	209 (78.3)	208 (78.5)	204 (76.7)	268 (76.4)
Black or African American	75 (6.1)	33 (4.1)	14 (5.2)	9 (3.4)	10 (3.8)	14 (4.0)
Asian	196 (15.9)	124 (15.5)	38 (14.2)	41 (15.5)	45 (16.9)	61 (17.4)
Other*	31 (2.5)	20 (2.6)	6 (2.3)	7 (2.9)	7 (2.9)	8 (2.2)
Ethnicity, n (%)						
Not Hispanic or Latino	981 (79.6)	617 (77.3)	200 (74.9)	203 (76.6)	214 (80.5)	283 (80.6)
Hispanic or Latino	246 (20.0)	179 (22.4)	65 (24.3)	62 (23.4)	52 (19.5)	67 (19.1)
Not reported or unknown	1 (0.1)	2 (0.3)	2 (0.7)	0	0	0
Disease duration, y, median (Q1, Q3)	17.6 (9.4, 28.3)	18.4 (9.3, 30.1)	17.6 (9.0, 30.1)	18.4 (10.0, 30.0)	19.5 (9.2, 30.2)	19.3 (10.0, 30.5)
IGA, n (%)						
Moderate	729 (59.1)	508 (63.7)	177 (66.3)	161 (60.8)	170 (63.9)	223 (63.5)
Severe	504 (40.9)	290 (36.3)	90 (33.7)	104 (39.2)	96 (36.1)	128 (36.5)
EASI, median (Q1, Q3)	27.9 (21.0, 37.8)	27.2 (20.8, 36.0)	26.9 (20.6, 37.2)	27.7 (21.3, 36.5)	27.2 (20.7, 35.1)	27.7 (21.3, 37.2)
Percentage of BSA affected by AD, median % (Q1, Q3)	45.5 (31.0, 63.0)	44.8 (30.2, 62.0)	43.0 (30.6, 60.0)	46.0 (29.7, 63.0)	46.0 (31.0, 63.5)	46.2 (31.6, 64.0)
PP-NRS, median severity (Q1, Q3)	8.0 (6.0, 9.0)	7.0 (6.0, 8.0)	7.0 (6.0, 9.0)	7.0 (6.0, 8.0)	7.5 (6.0, 9.0)	7.0 (6.0, 9.0)
PSAAD, n	1143	739	248	240	251	314
Median score (Q1, Q3)	5.5 (3.9, 7.1)	5.4 (3.8, 7.0)	5.5 (3.8, 6.9)	5.3 (4.0, 6.9)	5.2 (3.9, 7.3)	5.3 (3.8, 6.9)
SCORAD, n	1230	797	266	265	266	350
Median (Q1, Q3)	67.1 (57.7, 77.1)	66.3 (57.6, 76.0)	64.9 (57.4, 76.4)	67.8 (58.5, 75.8)	66.4 (56.8, 75.9)	66.3 (57.6, 76.2)
DLQI, n	965	639	210	216	213	279
Median (Q1, Q3)	16.0 (12.0, 21.0)	16.0 (12.0, 21.0)	16.0 (12.0, 21.0)	16.0 (11.0, 20.0)	16.0 (12.0, 22.0)	16.0 (12.0, 21.0)
CDLQI, n	235	140	46	48	46	62
Median (Q1, Q3)	12.0 (8.0, 16.0)	12.0 (7.5, 16.0)	12.5 (8.0, 19.0)	12.0 (8.0, 15.5)	10.0 (7.0, 15.0)	11.0 (7.0, 16.0)
POEM, n	1200	779	256	264	259	341
Median (Q1, Q3)	21.0 (16.0, 25.0)	21.0 (16.0, 25.0)	21.0 (17.0, 24.0)	20.0 (16.0, 24.0)	21.0 (17.0, 25.0)	21.0 (17.0, 24.0)
Prior medication						
No prior medication	4 (0.3)	1 (0.1)	0	1 (0.4)	0	1 (0.3)
Topical agents only†	487 (39.5)	322 (40.4)	102 (38.2)	118 (44.5)	102 (38.3)	125 (35.6)
Systemic agents‡	742 (60.2)	475 (59.5)	165 (61.8)	146 (55.1)	164 (61.7)	225 (65.1)
Nonbiologic	656 (53.2)	431 (54.0)	152 (56.9)	130 (49.1)	149 (56.0)	201 (57.3)
Biologic	86 (7.0)	44 (5.5)	13 (4.9)	16 (6.0)	15 (5.6)	24 (6.8)
Dupilumab	65 (5.3)	32 (4.0)	9 (3.4)	12 (4.5)	11 (4.1)	19 (5.4)
Other biologic agents	27 (2.2)	15 (1.9)	4 (1.5)	5 (1.9)	6 (2.3)	6 (1.7)

AD, Atopic dermatitis; *BSA*, body surface area; *CDLQI*, children's dermatology life quality index; *DLQI*, dermatology life quality index; *EASI*, eczema area and severity index; *IGA*, investigator global assessment; *POEM*, patient-oriented eczema measure; *PP-NRS*, peak pruritus numerical rating scale; *PSAAD*, pruritus and symptoms assessment for atopic dermatitis; *Q1*, quartile 1; *Q3*, quartile 3; *SCORAD*, SCORing atopic dermatitis.
*Other includes American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, multiracial, and not reported.
†Topical agents include corticosteroids, calcineurin inhibitors, and crisaborole.
‡Systemic agents include corticosteroids, cyclosporin, nonbiologic agents, and biologic agents.

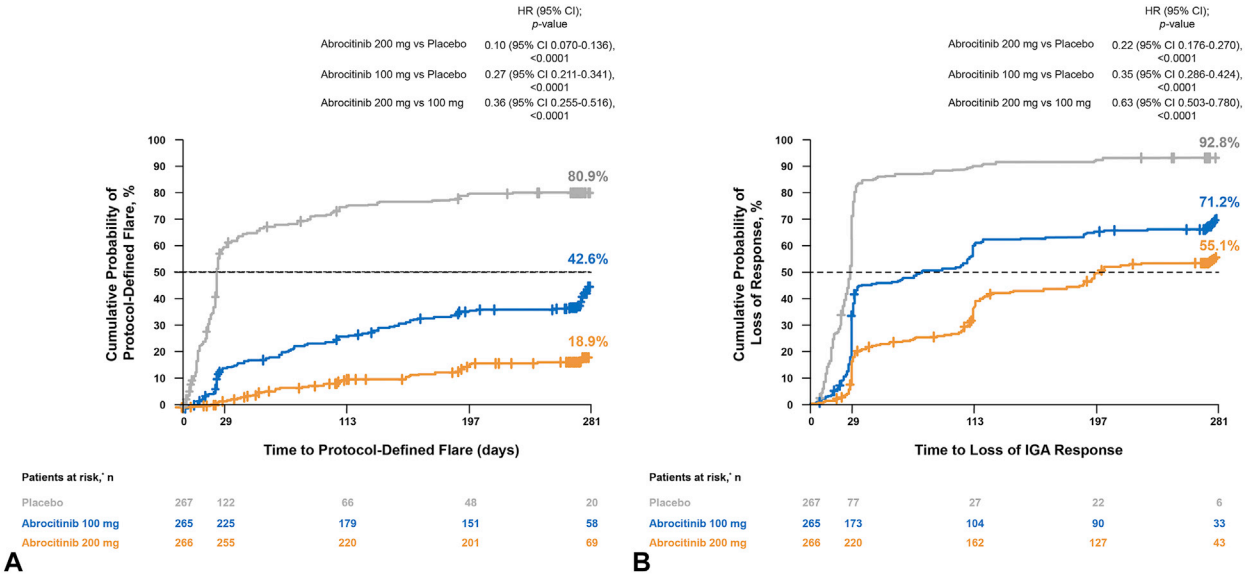

Fig 1. Time to event analyses. **A,** Time to protocol-defined flare. **B,** Time to first loss of response based on IGA ≥2. Per study protocol, flare was defined as a ≥50% loss of initial eczema area and severity index response at week 12 with a new IGA score ≥2. *HR*, Hazard ratio; *IGA*, investigator global assessment. *Patients who did not have a flare and were continuing treatment.

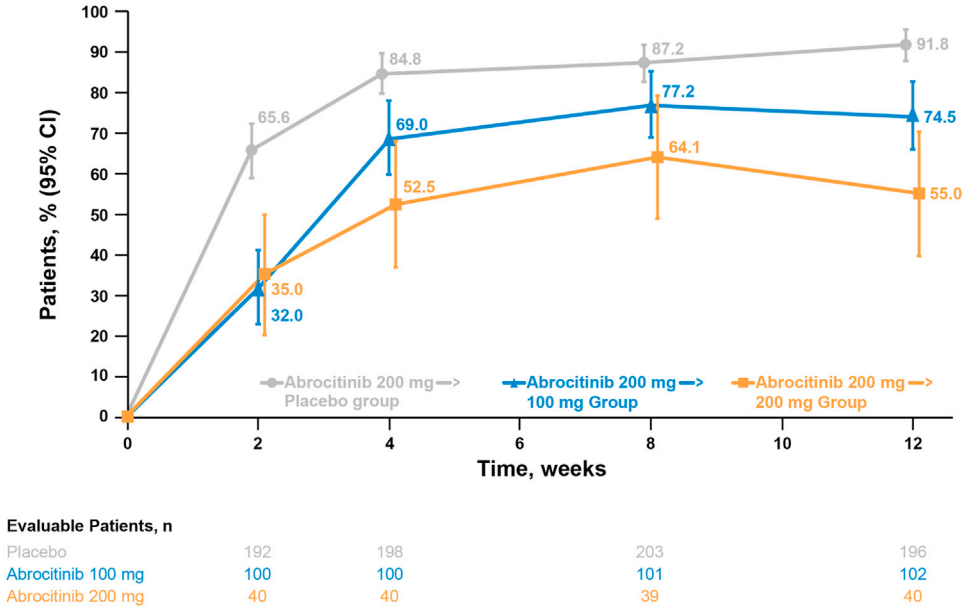

Fig 2. Proportion of patients who recaptured ≥75% improvement in eczema area and severity index response during the rescue period.

abrocitinib 100 mg, and placebo maintenance arms, respectively (Fig 2). The corresponding IGA 0/1 and PP-NRS-4 response recapture rates were 36.6%, 58.8%, and 81.6% (Supplemental Fig 7 available via Mendeley at https://data.mendeley.com/datasets/xjn2xnpk2h/1) and 30.0%, 35.3%, and 73.2%, respectively (Supplemental Fig 8 available via Mendeley at https://data.mendeley.com/datasets/xjn2xnpk2h/1.)

Patient-reported outcomes

Among induction responders who did not experience protocol-defined flare, improvements in patient-reported outcome measures, including the

Table II. Summary of patient year and incidence rates for treatment-emergent adverse events (any causality)

		Randomized maintenance				
			Abrocitinib			
	Induction	Placebo	100 mg	200 mg	All	Rescue
Treatment-emergent adverse event	n = 1233	n = 267	n = 265	n = 266	n = 798	n = 351
TEAEs occurring in ≥2% of patients, n (%)	512 (41.5)	87 (32.6)	67 (25.3)	92 (34.6)	246 (30.8)	97 (27.6)
Total drug exposure (PY)	209.36	53.31	130.25	145.81	329.37	86.34
Incidence rates (95% CI)	244.55 (223.82-266.68)	163.18 (130.70-201.29)	51.44 (39.86-65.32)	63.10 (50.87-77.38)	74.69 (65.64-84.63)	112.34 (91.10-137.05)
Serious infection, n (%)	6 (0.5)	2 (0.7)	2 (0.8)	5 (1.9)	9 (1.1)	1 (0.3)
Total drug exposure (PY)	309.90	62.86	148.97	183.97	395.79	107.28
Incidence rates (95% CI)	1.94 (0.71-4.21)	3.18 (0.39-11.49)	1.34 (0.16-4.85)	2.72 (0.88-6.34)	2.27 (1.04-4.32)	0.93 (0.02-5.19)
Herpes zoster infection, n (%)	9 (0.7)	2 (0.7)	2 (0.8)	9 (3.4)	13 (1.6)	8 (2.3)
Total drug exposure (PY)	309.54	62.37	148.88	181.13	392.38	106.17
Incidence rates (95% CI)	2.91 (1.33-5.52)	3.21 (0.39-11.58)	1.34 (0.16-4.85)	4.97 (2.27-9.43)	3.31 (1.76-5.67)	7.54 (3.25-14.85)

PY, Person years; *TEAE*, treatment-emergent adverse event.

SCORing atopic dermatitis sleep subscale, patient-oriented eczema measure, and pruritus and symptoms assessment in atopic dermatitis, showed evidence of dose response with maintenance abrocitinib (Supplemental Figs 9-11 available via Mendeley at https://data.mendeley.com/datasets/xjn2xnpk2h/1.)

Exposure and safety

In the maintenance period, median (range) exposure was 279 days (4-347 days), 273 days (5-323 days), and 27 days (3-318 days) in the abrocitinib 200 mg, abrocitinib 100 mg, and placebo groups, respectively. Because patients had variable drug exposure based on their treatment path through the 3 study periods, AEs were reported as IRs (patients per 100 patient years). The IRs of common treatment-emergent AEs (TEAEs; reported in ≥2%) were higher with abrocitinib 200 mg induction than with maintenance or flare treatment. In the maintenance period, patients receiving 100 mg of abrocitinib had a lower IR of TEAEs, serious infections, and herpes zoster infections than patients receiving 200 mg of abrocitinib (Table II).

Summaries of AEs, including treatment discontinuations and most common TEAEs by preferred term, are presented in Supplemental Tables II and III (available via Mendeley at https://data.mendeley.com/datasets/xjn2xnpk2h/1). In the abrocitinib 200 mg, abrocitinib 100 mg, and placebo maintenance groups, 6.0%, 1.9%, and 1.5%, respectively, discontinued treatment due to an AE. A nonfatal serious event of retinal vein thrombosis occurred, leading to discontinuation of 100 mg of abrocitinib during the maintenance period (additional detail in Supplemental Safety Narrative; available via Mendeley at https://data.mendeley.com/datasets/xjn2xnpk2h/1.)

Similar to other studies,[6,7,19] dose-related decreases in median platelet count were observed in abrocitinib-treated patients, with a nadir at week 4 and a return toward baseline values thereafter, followed by stabilization throughout the maintenance period (Supplemental Fig 12 available via Mendeley at https://data.mendeley.com/datasets/xjn2xnpk2h/1.) Recovery to baseline was more marked in patients randomly assigned to placebo. No patients discontinued treatment due to changes in platelet count. There were no clinically significant changes in hemoglobin, neutrophil, or lymphocyte counts. There were dose-related increases in cholesterol and high- and low-density lipoprotein levels for both abrocitinib doses compared with placebo during the first 4 weeks of treatment, but no clinically

significant changes in the high-density lipoprotein/low-density lipoprotein ratio.

DISCUSSION

Designed to assess both the probability of flaring during randomized dose reduction or withdrawal after initial response and the ability to recapture response in flaring patients, JADE REGIMEN was a unique phase 3 study in the clinical development landscape of moderate-to-severe AD. Most patients (64.7%) who received induction treatment with high-dose abrocitinib achieved IGA 0/1 and EASI-75 responses without the use of topical corticosteroids. Most of these initial responders who continued maintenance treatment with either abrocitinib 200 mg or 100 mg maintained their responses over 40 weeks of blinded follow-up. The probability of maintenance of response was higher for abrocitinib 200 mg versus 100 mg and for both abrocitinib doses versus placebo.

These observations support continuous abrocitinib 200 mg monotherapy as the most effective option for maintaining disease control. However, for most patients with moderate-to-severe AD, an induction-maintenance approach with abrocitinib 200 mg followed by 100 mg may be a viable strategy, given that the majority of patients receiving reduced-dose abrocitinib maintenance did not flare for at least 40 weeks. For patients who flare with either continuous abrocitinib 200 mg or reduced-dose abrocitinib (100 mg), abrocitinib 200 mg plus topical therapy is an acceptable approach to regain response. By contrast, intermittent therapy with treatment discontinuation after obtaining response may not be desirable for most patients, given the high rate of relapse. However, the identification of predictors for maintaining clinical response, as shown with psoriatic arthritis,[20] should continue to be explored.

Regarding safety, fewer TEAEs were reported in the abrocitinib 100 mg maintenance group versus the abrocitinib 200 mg maintenance group, suggesting a dose response in terms of AE occurrence as well as a lack of carryover effects from abrocitinib 200 mg induction. This will be an additional cost/risk-to-benefit consideration for determining the best maintenance dose for individual patients, especially among those with comorbidities or those at higher risk of infections.

Key limitations of this study were insufficient patient numbers to elucidate risk factors associated with flaring, lack of a previously established consensus on the definition of flare, open-label conduct of the induction and rescue periods, and lack of inclusion of patients with less-severe or episodic disease. Additional real-world and clinical data will be needed to refine the optimal dosing regimen for individual patients with moderate-to-severe AD over time.

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Conflicts of interest

Dr Blauvelt has served as a scientific adviser and/or clinical study investigator for Pfizer, AbbVie, Aligos, Almirall, Amgen, Arcutis, Arena, Athenex, Boehringer Ingelheim, Bristol Myers Squibb, Dermavant, Eli Lilly, Evommune, Forte, Galderma, Incyte, Janssen, Leo, Novartis, RAPT, Regeneron, Sanofi Genzyme, Sun Pharma, and UCB Pharma. Dr Silverberg has served as an investigator for AbbVie, Eli Lilly, Galderma, Kiniksa, LEO Pharma, and Trevi; as a consultant or advisory board member for Pfizer Inc, AbbVie, AFYX, Arena, Asana, BiomX, Bluefin, Bodewell, Boehringer Ingelheim, Celgene, Dermavant, Dermira, Eli Lilly, Galderma, GlaxoSmithKline, Incyte, Kiniksa, Leo, Luna, Menlo, Novartis, RAPT, Regeneron, and Sanofi; and as a speaker for Pfizer, Regeneron, and Sanofi. Dr Lynde has served as a principal investigator, consultant, and/or speaker for Pfizer Inc, AbbVie, Bausch Health (Valeant), Celgene, Eli Lilly, Janssen, LEO Pharma, and Novartis. Dr Bieber is a lecturer and/or consultant for Pfizer Inc, AbbVie, Almirall, AnaptysBio, Arena Pharmaceuticals, Asana Biosciences, BioVersys, Boehringer Ingelheim, Daiichi Sankyo, Dermavant Roivant, Eli Lilly, Galapagos/MorphoSys, Galderma, Glenmark, GSK, Incyte, Kymab, Leo, La Roche-Posay, Menlo Therapeutics, Novartis, RAPT, Sanofi Regeneron, UCB, and Vectans Pharma and an investigator for AFYX (DermTreat). Dr Eisman has been an investigator in clinical trials for Pfizer Inc, AbbVie, Arena, Boston Pharmaceuticals, Bristol Myers Squibb, Botanix, Dermira, Eli Lilly, Leo, Novartis, Regeneron, and Suzhou Connect Biopharmaceuticals. Dr Zdybski has been an investigator for clinical trials for Pfizer, Trevi Pharmaceuticals, and Regeneron. Dr Gubelin has served as a scientific adviser and/or clinical study investigator for Pfizer, Galderma, GSK, Eucerin, Johnson & Johnson, Janssen, Sanofi, BioNOOX, and Beiersdorf/Eucerin. Dr Simpson reports grants from Pfizer Inc, Eli Lilly, Kyowa Kirin, Leo, Merck, and Regeneron and personal fees from Pfizer Inc, Bausch Health (Valeant), Dermira, Eli Lilly, Galderma, Leo, Menlo Therapeutics, Novartis, Regeneron, and Sanofi Genzyme. Dr Valenzuela has served as a scientific adviser and/or clinical study investigator for Pfizer, AbbVie, Amgen, Eli Lilly, Galderma, Janssen, Leo, Merck, Novartis, and Sanofi Genzyme. Dr Criado reports grants from Abbott, Takeda, Novartis, and Pfizer. Dr Lebwohl is an employee of Mount

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REFERENCES

1. Boguniewicz M, Fonacier L, Guttman-Yassky E, Ong PY, Silverberg J, Farrar JR. Atopic dermatitis yardstick: practical recommendations for an evolving therapeutic landscape. *Ann Allergy Asthma Immunol*. 2018;120(1):10-22.
2. Bissonnette R, Iversen L, Sofen H, et al. Tofacitinib withdrawal and retreatment in moderate-to-severe chronic plaque psoriasis: a randomized controlled trial. *Br J Dermatol*. 2015;172(5):1395-1406.
3. Bao L, Zhang H, Chan LS. The involvement of the JAK-STAT signaling pathway in chronic inflammatory skin disease atopic dermatitis. *JAKSTAT*. 2013;2(3):e24137.
4. Ghoreschi K, Laurence A, O'Shea JJ. Janus kinases in immune cell signaling. *Immunol Rev*. 2009;228(1):273-287.
5. Mollanazar NK, Smith PK, Yosipovitch G. Mediators of chronic pruritus in atopic dermatitis: getting the itch out? *Clin Rev Allergy Immunol*. 2016;51(3):263-292.
6. Silverberg JI, Simpson EL, Thyssen JP, et al. Efficacy and safety of abrocitinib in patients with moderate-to-severe atopic dermatitis: a randomized clinical trial. *JAMA Dermatol*. 2020;156(8):863-873.
7. Simpson EL, Sinclair R, Forman S, et al. Efficacy and safety of abrocitinib in adults and adolescents with moderate-to-severe atopic dermatitis (JADE MONO-1): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet*. 2020;396(10246):255-266.
8. Thaci T, Bieber T, Simpson EL, et al. A phase 3 study to investigate the efficacy and safety of abrocitinib and dupilumab in comparison with placebo in adults with moderate-to-severe atopic dermatitis. Paper presented at: 29th EADV Congress; October 28-November 1, 2020; EADV Virtual.
9. Bieber T, Simpson EL, Silverberg J, et al. Abrocitinib versus placebo and dupilumab for atopic dermatitis. *N Engl J Med*. 2021;384(12):1101-1112.
10. Eichenfield LE, Flohr C, Sidbury R, et al. Efficacy and safety of abrocitinib in adolescent patients with moderate-to-severe atopic dermatitis (AD): results from the phase 3 JADE TEEN study. *J Allergy Clin Immunol*. 2021;147(2):AB146.
11. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol*. 1980;60(92):44-47.
12. Hanifin JM, Thurston M, Omoto M, et al. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. *Exp Dermatol*. 2001;10(1):11-18.
13. Yosipovitch G, Reaney M, Mastey V, et al. Peak pruritus numerical rating scale: psychometric validation and responder definition for assessing itch in moderate-to-severe atopic dermatitis. *Br J Dermatol*. 2019;181(4):761-769.
14. Stalder JF, Taieb A, Atherton DJ, et al. Severity scoring of atopic dermatitis: the SCORAD index: consensus report of the European Task Force on atopic dermatitis. *Dermatology*. 1993;186(1):23-31.
15. Finlay AY, Khan GK. Dermatology life quality index (DLQI): a simple practical measure for routine clinical use. *Clin Exp Dermatol*. 1994;19(3):210-216.
16. Lewis-Jones MS, Finlay AY. The children's dermatology life quality index (CDLQI): initial validation and practical use. *Br J Dermatol*. 1995;132(6):942-949.
17. Charman CR, Venn AJ, Williams HC. The patient-oriented eczema measure: development and initial validation of a new tool for measuring atopic eczema severity from the patients' perspective. *Arch Dermatol*. 2004;140(12):1513-1519.
18. Lebwohl MG, Simpson EL, Bushmakin AG, et al. Validation of the pruritus and symptoms assessment for atopic dermatitis in adults with moderate to severe atopic dermatitis. Paper presented at: 10th Georg Rajka International Symposium on Atopic Dermatitis; April 11, 2018; Utrecht, Netherlands.
19. Soto E, Banfield C, Gupta P, Peterson MC. Kinetic-pharmacodynamic model of platelet time course in patients with moderate-to-severe atopic dermatitis treated with oral janus kinase 1 inhibitor abrocitinib. *CPT Pharmacometrics Syst Pharmacol*. 2020;9(10):553-560.
20. Coates LC, Cook R, Lee KA, Chandran V, Gladman DD. Frequency, predictors, and prognosis of sustained minimal disease activity in an observational psoriatic arthritis cohort. *Arthritis Care Res*. 2010;62(7):970-976.