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Efficacy and Safety of Abrocitinib in Patients With Moderate-to-Severe Atopic Dermatitis

A Randomized Clinical Trial

Jonathan I. Silverberg, MD, PhD, MPH; Eric L. Simpson, MD; Jacob P. Thyssen, MD; Melinda Gooderham, MSc, MD; Gary Chan, PharmD; Claire Feeney, PhD; Pinaki Biswas, PhD; Hernan Valdez, MD; Marco DiBonaventura, PhD; Chudy Nduaka, DVM, PhD; Ricardo Rojo, MD

IMPORTANCE Abrocitinib, an oral, once-daily Janus kinase 1 selective inhibitor, was effective and well tolerated in a phase 3 monotherapy trial of patients with moderate-to-severe atopic dermatitis (AD).

OBJECTIVE To investigate the efficacy and safety of abrocitinib in adolescents and adults with moderate-to-severe AD in an identically designed trial.

DESIGN, SETTING, AND PARTICIPANTS This phase 3, double-blinded, placebo-controlled, parallel-group randomized clinical trial included patients 12 years or older with a clinical diagnosis of moderate-to-severe AD for at least 1 year and inadequate response to topical medications given for at least 4 weeks within 6 months. Patients were enrolled from 115 centers in Australia, Bulgaria, Canada, China, Czechia, Germany, Hungary, Japan, South Korea, Latvia, Poland, United Kingdom, and the United States from June 29, 2018, to August 13, 2019. Data were analyzed from September 13 to October 25, 2019.

INTERVENTIONS Patients were randomly assigned (2:2:1) to receive once-daily oral abrocitinib in 200- or 100-mg doses or placebo for 12 weeks.

MAIN OUTCOMES AND MEASURES The coprimary end points were the proportion of patients achieving Investigator Global Assessment (IGA) response (ie, clear [0] or almost clear [1], with improvement of ≥ 2 grades) and the proportion of patients achieving at least 75% improvement in Eczema Area and Severity Index score (EASI-75) at week 12. Key secondary end points included the proportion of patients achieving a Peak Pruritus Numerical Rating Scale (PP-NRS) response (ie, improvement of ≥ 4 points) at week 12. Other secondary end points included the proportion of patients achieving at least 90% improvement in EASI score (EASI-90). Safety was assessed via adverse events and laboratory monitoring.

RESULTS A total of 391 patients (229 male [58.6%]; mean [SD] age, 35.1 [15.1] years) were included in the analysis; of these, 155 received abrocitinib, 200 mg/d; 158, abrocitinib, 100 mg/d; and 78, placebo. Among patients with available data at week 12, greater proportions of patients in the 200- and 100-mg abrocitinib groups vs the placebo group achieved IGA (59 of 155 [38.1%] and 44 of 155 [28.4%] vs 7 of 77 [9.1%]; $P < .001$) and EASI-75 (94 of 154 [61.0%] and 69 of 155 [44.5%] vs 8 of 77 [10.4%]; $P < .001$), greater estimated proportions achieved PP-NRS (55.3% [95% CI, 47.2%-63.5%] and 45.2% [95% CI, 37.1%-53.3%] vs 11.5% [95% CI, 4.1%-19.0%]; $P < .001$), and/or greater proportions achieved EASI-90 (58 of 154 [37.7%] and 37 of 155 [23.9%] vs 3 of 77 [3.9%]) responses. Adverse events were reported for 102 patients (65.8%) in the 200-mg group, 99 (62.7%) in the 100-mg group, and 42 (53.8%) in the placebo group; serious adverse events were reported for 2 patients (1.3%) in the 200-mg group, 5 (3.2%) in the 100-mg group, and 1 (1.3%) in the placebo group. Decreases in platelet count (2 [1.3%]) and laboratory values indicating thrombocytopenia (5 [3.2%]) were reported in the 200-mg group.

CONCLUSIONS AND RELEVANCE Monotherapy with once-daily oral abrocitinib was effective and well tolerated in adolescents and adults with moderate-to-severe AD.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: [NCT03575871](https://clinicaltrials.gov/ct2/show/study/NCT03575871)

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Author Affiliations: Department of Dermatology, The George Washington University School of Medicine and Health Sciences, Washington, DC (Silverberg); Department of Dermatology, Oregon Health & Science University, Portland (Simpson); Department of Dermatology and Allergy, Herlev-Gentofte Hospital, University of Copenhagen, Hellerup, Denmark (Thyssen); SKiN Centre for Dermatology, Queen's University and Probitry Medical Research, Peterborough, Ontario, Canada (Gooderham); Pfizer Inc, Groton, Connecticut (Chan, Rojo); Pfizer Ltd, Surrey, United Kingdom (Feeney); Pfizer Inc, New York, New York (Biswas, Valdez, DiBonaventura); Pfizer Inc, Collegeville, Pennsylvania (Nduaka).

Corresponding Author: Hernan Valdez, MD, Pfizer Inc, 235 E 42nd St, New York, NY 10017 (herman.valdez@pfizer.com).

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin condition with immune dysfunction that affects lesional and nonlesional skin.¹ It is characterized by pruritus, skin pain, eczematous lesions, and dry skin.²⁻⁵ Atopic dermatitis affects as many as 20% of children and adolescents and approximately 5% to 10% of adults⁶⁻⁹ and is associated with substantial comorbidity and impairment in patient and caregiver quality of life.^{10,11}

Systemic therapy is used to treat patients with moderate-to-severe AD on failure or excessive use of topical treatments. Immunosuppressive agents can have modest efficacy in patients with moderate-to-severe AD but are associated with adverse events that often limit long-term use.¹² Dupilumab, a subcutaneous interleukin 4 (IL-4) receptor- α subunit antagonist that blocks IL-4 and IL-13 signaling, is approved to treat patients with moderate-to-severe AD. Not all patients respond to dupilumab, and some lose response to treatment over time.¹³ Dupilumab use is limited in patients unwilling to receive injections, as is the potential for flexible or episodic treatment. Furthermore, dupilumab treatment is associated with injection site reactions, conjunctivitis,¹⁴ and/or face and neck erythema.¹⁵ Hence, additional treatments for patients with moderate-to-severe AD are needed.

Abrocitinib is an oral, once-daily Janus kinase 1 (JAK1) selective inhibitor under investigation for the treatment of AD. Selective inhibition of JAK1 with abrocitinib modulates signaling by IL-4, IL-13, and other cytokines (eg, IL-31, IL-22, and thymic stromal lymphopoietin) involved in the pathogenesis of AD and pruritus while sparing JAK2 inhibition and minimizing the risk for neutropenia and anemia.¹⁶ Inhibition of neuronal JAK1 pathways has also been shown to ameliorate pruritus.¹⁷ Monotherapy with once-daily abrocitinib in 200-mg or 100-mg oral doses was effective and well tolerated in a dose-ranging phase 2b study in adults with moderate-to-severe AD.¹⁸ Similar results were observed in JADE MONO-1, a phase 3 trial of abrocitinib (200 mg or 100 mg) vs placebo in adolescents and adults with moderate-to-severe AD.^{19,20} Herein, we report the results of JADE MONO-2, a second replicate phase 3 trial of monotherapy with once-daily oral abrocitinib (200 mg or 100 mg) vs placebo in patients 12 years or older with moderate-to-severe AD.

Methods

The study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki²¹ and in compliance with all International Council for Harmonisation Good Clinical Practice Guidelines.²² All local regulatory requirements were followed. This research was approved by institutional review boards or ethics committees at each study site. An external data monitoring review committee monitored the safety of patients throughout the study. All patients or parents and guardians provided written informed consent. There were no substantial changes to methods or trial outcomes after the study was initiated. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Key Points

Question What is the efficacy and safety of abrocitinib monotherapy in patients with moderate-to-severe atopic dermatitis?

Findings In this randomized clinical trial of 391 patients 12 years or older with moderate-to-severe atopic dermatitis, significantly greater proportions of patients treated with abrocitinib (200 mg or 100 mg) compared with placebo achieved an Investigator Global Assessment response of clear or almost clear with improvement of at least 2 grades and/or at least 75% improvement in Eczema Area and Severity Index scores. Serious adverse events were reported for 2 patients (1.3%) in the 200-mg group, 5 (3.2%) in the 100-mg group, and 1 (1.3%) in the placebo group.

Meaning Abrocitinib was effective and well tolerated in adolescents and adults with moderate-to-severe atopic dermatitis.

Study Design and Participants

This multicenter, international, phase 3, placebo-controlled, parallel-group randomized clinical trial was conducted from June 29, 2018, to August 13, 2019, in Australia, Bulgaria, Canada, China, Czechia, Germany, Hungary, Japan, South Korea, Latvia, Poland, United Kingdom, and the United States. Eligible patients were 12 years or older, with body weight of at least 40 kg. Adolescent patients younger than 18 years (or country-specific age of majority) were eligible on a country-by-country basis as approved by the country or regulatory/health authority. Eligible patients had a confirmed diagnosis of chronic AD²³ for at least 1 year before the first dose of study drug and moderate-to-severe AD (Investigator's Global Assessment [IGA] score ≥ 3 , Eczema Area and Severity Index [EASI] score²⁴ ≥ 16 , affected body surface area $\geq 10\%$, and Peak Pruritus Numerical Rating Scale [PP-NRS, used with permission of Regeneron Pharmaceuticals, Inc, and Sanofi SA] score²⁵ ≥ 4) at the baseline visit. Eligible patients also had a documented recent history (within 6 months before screening) of inadequate response to treatment with topical corticosteroids or topical calcineurin inhibitors given for at least 4 weeks, a history of topical AD treatments being considered medically inadvisable, or a history of receiving systemic therapies for AD. The study protocol is found in [Supplement 1](#).

Patients with a medical history of conditions associated with thrombocytopenia, coagulopathy, or platelet dysfunction were excluded from the study. Patients who had used any systemic JAK inhibitor, had used a systemic corticosteroid within 4 weeks of the first dose of study medication, had used topical treatments for AD within 72 hours of the first dose of study medication, or had received treatment with dupilumab within 6 weeks of the first dose of study medication were excluded. Concomitant use of topical (corticosteroids, calcineurin inhibitors, tars, antibiotic creams, or topical antihistamines) or systemic therapies for AD or rescue medication was prohibited. Patients were permitted to use oral antihistamines and topical nonmedicated emollients. Additional exclusion criteria are presented in eMethods in [Supplement 2](#).

Randomization and Masking

Patients were randomly assigned (2:2:1) to receive once-daily oral abrocitinib in 200-mg or 100-mg doses or matching placebo for 12 weeks with a computer-generated randomization schedule using interactive response technology (Almac Group). Randomization was stratified by baseline disease severity (IGA score of 3 or 4) and age group (<18 or ≥18 years) and was administered via an interactive response technology system. Patients, investigators, and sponsors were blinded to study treatment.

Outcomes Measures

Multiplicity-controlled coprimary end points were the proportion of patients achieving IGA response (clear [0] or almost clear [1] with an improvement of ≥2 grades from baseline) and proportion of patients achieving EASI-75 response (≥75% improvement from baseline), both at week 12. Multiplicity-controlled key secondary end points were the proportion of patients achieving PP-NRS response (improvement of ≥4 points from baseline) at weeks 2, 4, and 12 and change from baseline in Pruritus and Symptoms Assessment for AD (an 11-item questionnaire developed to measure daily symptoms of AD) total score²⁶ at week 12.

Other secondary end points included the proportion of patients achieving IGA response at all other scheduled points, the proportion of patients achieving EASI-75 at all other scheduled points, the proportion of patients achieving EASI-50 response (improvement of ≥50% from baseline) and/or EASI-90 response (improvement of ≥90% from baseline) at all scheduled points, the proportion of patients with PP-NRS response at all other scheduled points, time to PP-NRS response, and change from baseline in Scoring of AD index²⁷ and EASI scores at all scheduled points.

The incidence of adverse events and clinical abnormalities as well as changes from baseline in clinical laboratory values, electrocardiographic measurements, and vital signs were recorded from the first dose of study drug through 28 days after the last dose of study drug. Patient-reported outcomes included change from baseline at week 12 and all other points in Dermatology Life Quality Index (DLQI) total score²⁸ (in patients aged ≥18 years); Children's DLQI (CDLQI) total score²⁹ (in patients aged <18 years), Patient-Oriented Eczema Measure total score,³⁰ Patient Global Assessment score, and Hospital Anxiety and Depression Scale anxiety and depression scores.³¹

Statistical Analysis

Data were analyzed from September 13 to October 25, 2019. Sample size calculation was based on Fisher exact test for comparing 2 proportions (eMethods in Supplement 2). The family-wise type 1 error rate for testing the coprimary and key secondary end points was strictly controlled at 5% using a sequential, Bonferroni-based procedure (eFigure 1 in Supplement 2). Testing of all other secondary end points was performed at the nominal 5% significance level and not controlled for multiplicity. Additional details of the statistical analysis are presented in eMethods in Supplement 2. Two-sided $P < .05$ indicated significance. Binary end points were

tested with the Cochran-Mantel-Haenszel test. Continuous measures were tested based on a t distribution.

Results

Patients

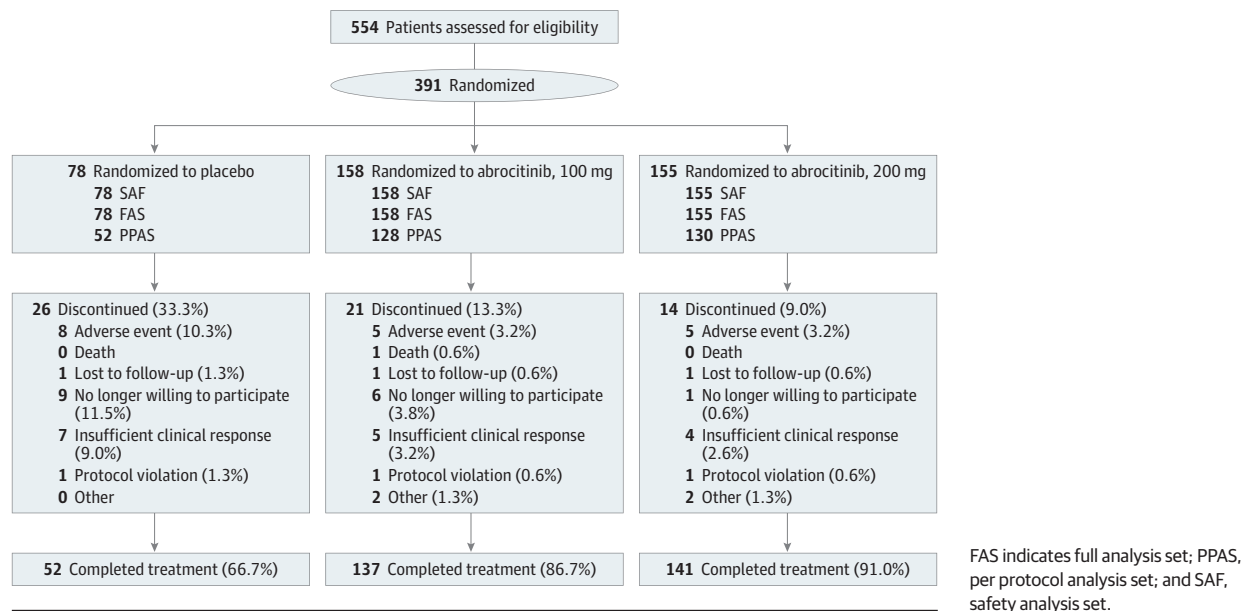
Overall, 554 patients were screened and 391 were randomized to treatment groups (229 male [58.6%] and 162 female [41.4%]; mean [SD] age, 35.1 [15.1] years). The treatment discontinuation rate was higher in the placebo group (26 of 78 [33.3%]) than in the abrocitinib groups (200-mg group, 14 of 155 [9.0%]; 100-mg group, 21 of 158 [13.3%]) (Figure 1).

Demographics and baseline characteristics were balanced across treatment arms (Table 1). White (232 [59.3%]), Asian (129 [33.0%]), black (21 [5.4%]), and Hispanic (9 [2.3%]) patients were included. Overall, 265 patients (67.8%) had moderate disease and 126 (32.2%) had severe disease, assessed by IGA score; 162 (41.4%) had received systemic treatment with or without topical treatment; and 226 (57.8%) had received topical agents alone within 1 year before the current study.

Efficacy

Among patients with data available at week 12 for the efficacy analysis, 59 of 155 patients in the 200-mg group (38.1%), 44 of 155 in the 100-mg group (28.4%), and 7 of 77 in the placebo group (9.1%) had an IGA response (Figure 2A); differences from placebo were 28.7% (95% CI, 18.6%-38.8%; $P < .001$) for the 200-mg group and 19.3% (95% CI, 9.6%-29.0%; $P < .001$) for the 100-mg group (eTable 1 in Supplement 2). At week 12, 94 of 154 patients in the 200-mg group (61.0%), 69 of 155 in the 100-mg group (44.5%), and 8 of 77 in the placebo group (10.4%) had an EASI-75 response (Figure 2B); differences from placebo were 50.5% (95% CI, 40.0%-60.9%; $P < .001$) for the 200-mg group and 33.9% (95% CI, 23.3%-44.4%; $P < .001$) for the 100-mg group (eTable 1 in Supplement 2). Sensitivity analyses performed for the coprimary end points at week 12 yielded similar conclusions (IGA response in the per protocol analysis set, 50 of 130 in the 200-mg group [38.5%], 39 of 128 in the 100-mg group [30.5%], and 6 of 52 in the placebo group [11.5%]; EASI-75 response in the per protocol analysis set, 81 of 130 in the 200-mg group [62.3%], 63 of 128 in the 100-mg group [49.2%], and 7 of 52 in the placebo group [13.5%]) (eTables 2 and 3 in Supplement 2). The proportions of patients achieving IGA (<18 years, 6 of 15 in the 200-mg group [40.0%], 2 of 16 patients in the 100-mg group [12.5%], and 0 of 7 patients in the placebo group [0%]; ≥18 years, 53 of 140 in the 200-mg group [37.9%], 42 of 139 patients in the 100-mg group [30.2%], and 7 of 70 patients in the placebo group [10.0%]) and/or EASI-75 (<18 years, 9 of 15 in the 200-mg group [60.0%], 7 of 16 patients in the 100-mg group [43.8%], and 0 of 7 patients in the placebo group [0%]; ≥18 years, 85 of 139 in the 200-mg group [61.2%], 62 of 139 patients in the 100-mg group [44.6%], and 8 of 70 patients in the placebo group [11.4%]) responses were higher with abrocitinib treatment vs placebo for all age groups (eTable 4 in Supplement 2). From weeks 2 to 12, the proportions of patients achieving IGA (week 2, 22 of 152 in the 200-mg group [14.5%], 8 of 157 in the 100-mg group [5.1%],

Figure 1. CONSORT Diagram



and 0 of 76 in the placebo group; week 12, 59 of 155 in the 200-mg group [38.1%], 44 of 155 in the 100-mg group [28.4%], and 7 of 77 in the placebo group [9.1%] and/or EASI-75 (week 2, 37 of 152 in the 200-mg group [24.3%], 16 of 157 in the 100-mg group [10.2%], and 1 of 76 in the placebo group [1.3%]; week 12, 94 of 154 in the 200-mg group [61.0%], 69 of 155 in the 100-mg group [44.5%], and 8 of 77 in the placebo group [10.4%]) responses increased and were higher for abrocitinib at each time point than with placebo (Figure 2).

Percentage decreases from baseline in EASI scores were greater for both abrocitinib doses than for placebo at all time points (week 2, -51.3 [95% CI, -55.9 to -46.7] in the 200-mg group, -39.2 [95% CI, -43.8 to -34.7] in the 100-mg group, and -9.0 [95% CI, -15.4 to -2.5] in the placebo group; week 12, -73.3 [95% CI, -79.7 to -66.9] in the 200-mg group, -60.0 [95% CI, -66.5 to -53.6] in the 100-mg group, and -28.6 [95% CI, -38.4 to -18.8] in the placebo group) (eFigure 2A in Supplement 2). From weeks 2 to 12, the proportions of patients achieving EASI-50 (week 2, 84 of 152 in the 200-mg group [55.3%], 56 of 157 in the 100-mg group [35.7%], and 8 of 76 in the placebo group [10.5%]; week 12, 123 of 154 in the 200-mg group [79.9%], 106 of 155 in the 100-mg group [68.4%], and 15 of 77 in the placebo group [19.5%]) and/or EASI-90 (week 2, 14 of 152 in the 200-mg group [9.2%], 4 of 157 in the 100-mg group [2.5%], and 0 of 76 in the placebo group; week 12, 58 of 154 in the 200-mg group [37.7%], 37 of 155 in the 100-mg group [23.9%], and 3 of 77 in the placebo group [3.9%]) responses increased and were higher for abrocitinib treatment groups at each point than for placebo (eTable 1 and eFigure 3 in Supplement 2).

Proportions of patients achieving a PP-NRS response increased from weeks 2 to 12 for both abrocitinib doses (estimated response rate at week 2, 35.3% [95% CI, 27.7%-42.9%] in the 200-mg group, 23.1% [95% CI, 16.5%-29.7%]

in the 100-mg group, and 3.9% [95% CI, 0.0%-8.3%] in the placebo group; estimated response rate at week 12, 55.3% [95% CI, 47.2%-63.5%] in the 200-mg group, 45.2% [95% CI, 37.1%-53.3%] in the 100-mg group, and 11.5% [95% CI, 4.1%-19.0%] in the placebo group) (Figure 3A and eTable 1 in Supplement 2). Decreases from baseline in PP-NRS scores were greater for both abrocitinib groups than the placebo group at all time points (week 12, -4.0 [95% CI, -4.4 to -3.6] in the 200-mg group, -3.3 [95% CI, -3.7 to -2.8] in the 100-mg group, and -1.6 [95% CI, -2.3 to -0.9] in the placebo group). Significant differences in PP-NRS scores between both doses of abrocitinib and placebo were observed within 24 hours of the first dose of treatment (ie, by day 2; -0.7 [95% CI, -0.9 to -0.5] in the 200-mg group, -0.6 [95% CI, -0.8 to -0.4] in the 100-mg group, and -0.1 [95% CI, -0.4 to 0.2] in the placebo group; $P < .05$ for 200-mg and 100-mg compared with placebo groups) (Figure 3B). Median time to PP-NRS response was 29.0 (95% CI, 16.0-31.0) days in the 200-mg group, 58.0 (95% CI, 56.0-83.0) days in the 100-mg group, and 112.0 (95% CI, 112.0-not evaluable [NE]) in the placebo group (Figure 3C). Decreases from baseline in Pruritus and Symptoms Assessment for AD (week 12, -3.0 [95% CI, -3.3 to -2.7] in the 200-mg group, -2.4 [95% CI, -2.8 to -2.1] in the 100-mg group, and -0.8 [95% CI, -1.3 to -0.3] in the placebo group) and Scoring of AD (week 12, -56.2 [95% CI, -61.2 to -51.1] in the 200-mg group, -45.8 [95% CI, -50.9 to -40.7] in the 100-mg group, and -22.7 [95% CI, -30.4 to -15.1] in the placebo group) index scores were greater for both abrocitinib groups vs placebo group at all points (eFigure 2B-C in Supplement 2).

Safety

Overall, 102 patients in the 200-mg group (65.8%), 99 in the 100-mg group (62.7%), and 42 in the placebo group (53.8%) reported treatment-emergent adverse events (TEAEs) of any

Table 1. Demographic and Baseline Characteristics

Characteristic	Treatment group ^a			All (n = 391)
	Placebo (n = 78)	Abrocitinib 100 mg (n = 158)	200 mg (n = 155)	
Age, mean (SD), y	33.4 (13.8)	37.4 (15.8)	33.5 (14.7)	35.1 (15.1)
Age group, y				
<18	8 (10.3)	17 (10.8)	15 (9.7)	40 (10.2)
18-64	69 (88.5)	130 (82.3)	133 (85.8)	332 (84.9)
≥65	1 (1.3)	11 (7.0)	7 (4.5)	19 (4.9)
Male	47 (60.3)	94 (59.5)	88 (56.8)	229 (58.6)
Race				
White	40 (51.3)	101 (63.9)	91 (58.7)	232 (59.3)
Asian	29 (37.2)	46 (29.1)	54 (34.8)	129 (33.0)
Black or African American	6 (7.7)	9 (5.7)	6 (3.9)	21 (5.4)
Multiracial	1 (1.3)	1 (0.6)	2 (1.3)	4 (1.0)
Not reported	2 (2.6)	1 (0.6)	2 (1.3)	5 (1.3)
Ethnicity				
Not Hispanic or Latino	73 (93.6)	154 (97.5)	150 (96.8)	377 (96.4)
Hispanic or Latino	2 (2.6)	3 (1.9)	4 (2.6)	9 (2.3)
Not reported	3 (3.8)	1 (0.6)	1 (0.6)	5 (1.3)
Disease duration, mean (SD), y	21.7 (14.3)	21.1 (14.8)	20.5 (14.8)	21.0 (14.7)
Prior prescribed or OTC medication for AD ^b				
Any	78 (100)	157 (99.4)	153 (98.7)	388 (99.2)
Anti-inflammatory topical agents alone (corticosteroids, crisaborole, calcineurin inhibitors)	46 (59.0)	87 (55.1)	93 (60.0)	226 (57.8)
Systemic agents (corticosteroids, cyclosporin, nonbiologics), biologics, and/or topical agents	32 (41.0)	70 (44.3)	60 (38.7)	162 (41.4)
Dupilumab	2 (2.6)	7 (4.4)	5 (3.2)	14 (3.6)
IGA score ^c				
3	52 (66.7)	107 (67.7)	106 (68.4)	265 (67.8)
4	26 (33.3)	51 (32.3)	49 (31.6)	126 (32.2)
EASI score, mean (SD) ^d	28.0 (10.2)	28.4 (11.2)	29.0 (12.4)	28.5 (11.5)
BSA affected, mean (SD), %	48.2 (20.8)	48.7 (21.4)	47.7 (22.3)	48.2 (21.6)
SCORAD				
No. of patients	78	158	155	391
Mean (SD) score ^e	64.3 (12.4)	63.8 (11.4)	64.1 (13.1)	64.0 (12.3)
PP-NRS				
No. of patients	78	158	155	391
Mean (SD) score ^f	6.7 (1.9)	7.1 (1.6)	7.0 (1.6)	7.0 (1.7)
PSAAD				
No. of patients	77	156	155	388
Mean (SD) total score ^g	5.1 (2.1)	5.4 (2.1)	5.2 (2.0)	5.2 (2.1)
DLQI ^h				
No. of patients	70	140	139	349
Mean (SD) total score ⁱ	15.0 (7.1)	15.4 (7.3)	14.8 (6.0)	15.0 (6.8)
CDLQI ^j				
No. of patients	8	16	15	39
Mean (SD) total score ^k	10.1 (3.8)	13.8 (5.8)	12.9 (5.7)	12.7 (5.4)
POEM				
No. of patients	78	156	154	388
Mean (SD) total score ^l	19.2 (5.5)	20.9 (5.7)	19.7 (5.7)	20.1 (5.7)

(continued)

Table 1. Demographic and Baseline Characteristics (continued)

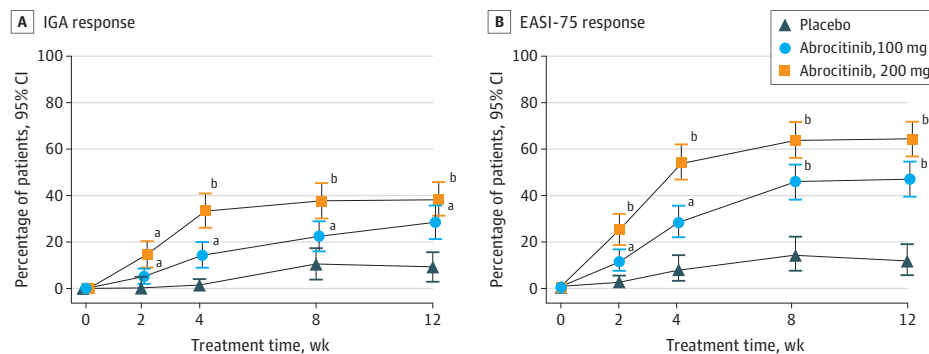
Characteristic	Treatment group ^a			All (n = 391)
	Placebo (n = 78)	Abrocitinib 100 mg (n = 158)	200 mg (n = 155)	
HADS				
Anxiety				
No. of patients	78	156	153	387
Mean (SD) score ^m	6.0 (3.7)	5.5 (4.2)	5.9 (3.9)	5.7 (4.0)
Depression				
No. of patients	78	156	153	387
Mean (SD) score ⁿ	4.4 (3.3)	4.1 (4.0)	4.0 (3.7)	4.1 (3.8)

Abbreviations: AD, atopic dermatitis; BSA, body surface area; CDLQI, Children's Dermatology Life Quality Index (DLQI); EASI, Eczema Area and Severity Index; HADS, Hospital Anxiety and Depression Scale; IGA, Investigator's Global Assessment; OTC, over-the-counter; POEM, Patient-Oriented Eczema Measure; PP-NRS, Peak Pruritus Numerical Rating Scale; PSAAD, Pruritus and Symptoms Assessment for Atopic Dermatitis; SCORAD, Scoring of Atopic Dermatitis index.

- ^a Unless otherwise indicated, data are expressed as number (percentage) of patients.
- ^b Patients were counted once for each main category in an exclusive manner, with systemic agents, biologics, and/or topical agents taking precedence over anti-inflammatory topical agents alone.
- ^c Scores range from 0 (clear) to 4 (severe), with 3 indicating moderate.
- ^d Scores range from 0 to 72, with higher scores indicating greater extent and severity of atopic dermatitis.
- ^e Scores range from 0 to 103, with higher scores indicating greater extent and

- severity of atopic dermatitis.
- ^f Scores range from 0 to 10, with higher scores indicating worse itch.
- ^g Scores range from 0 to 10, with higher scores indicating worse daily symptoms of atopic dermatitis.
- ^h For patients 18 years or older.
- ⁱ Scores range from 0 to 30, with higher scores indicating worse quality of life.
- ^j For patients aged younger than 18 years.
- ^k Scores range from 0 to 30, with higher scores indicating worst quality of life.
- ^l Scores range from 0 to 28, with higher scores indicating higher severity of atopic dermatitis.
- ^m Scores range from 0 to 21, with higher scores indicating increased anxiety.
- ⁿ Scores range from 0 to 21, with higher scores indicating increased depression.

Figure 2. Coprimary End Points at Week 12



Data are represented as the percentage of patients achieving Investigator Global Assessment (IGA) response (ie, clear [0] or almost clear [1], with improvement of ≥ 2 grades) and at least 75% improvement in Eczema Area and Severity Index (EASI-75) score from baseline. IGA response (A) was achieved in 38.1% of patients in the 200-mg group (59 of 155), 28.4% in the 100-mg group (44 of 155), and 9.1% in the placebo group (7 of 77). EASI-75 response (B) was achieved by 61.0% in the 200-mg group (94 of 154), 44.5% in the 100-mg

group (69 of 155), and 10.4% in the placebo group (8 of 77). Error bars represent 95% CIs. Conclusion of statistical significance was controlled for multiplicity only at week 12.

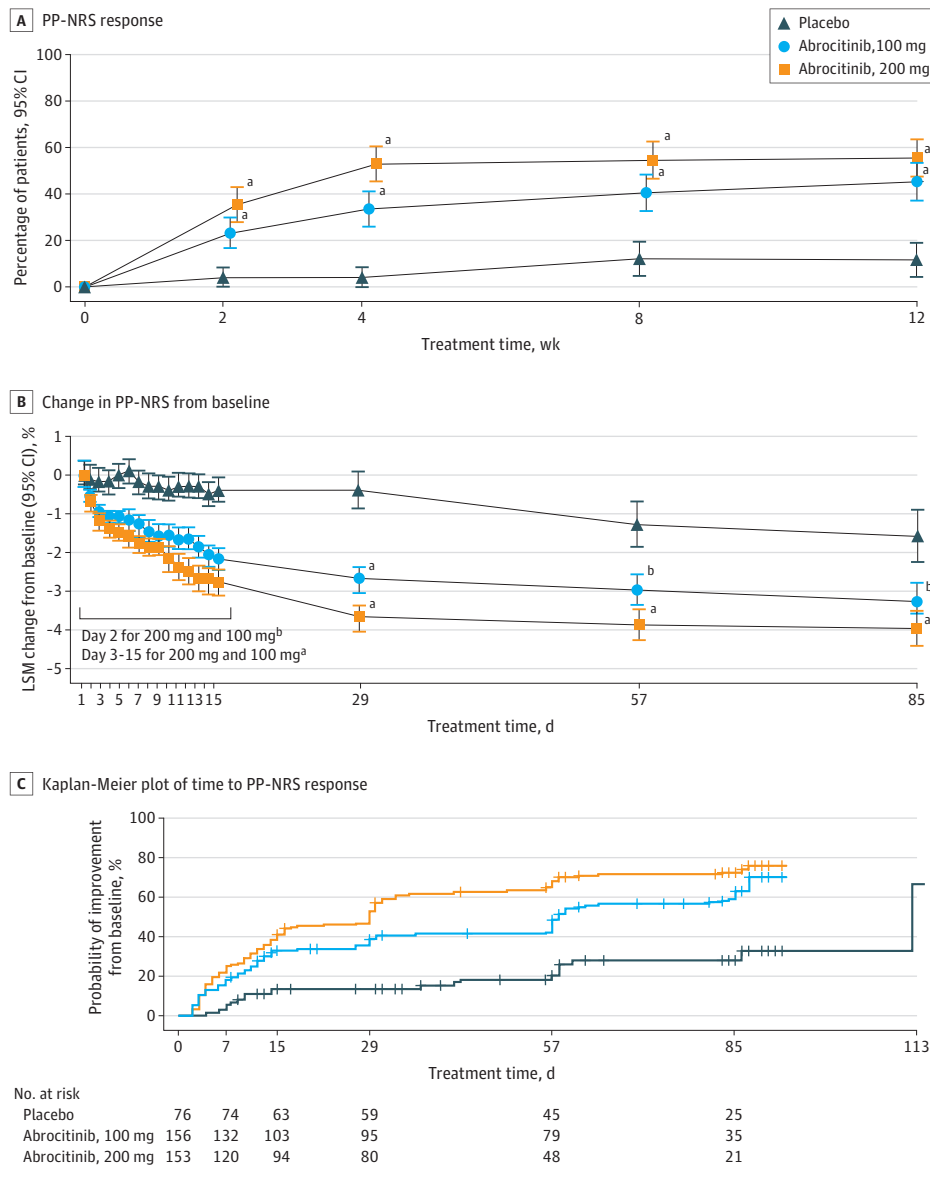
- ^a $P < .05$ vs placebo.
- ^b $P < .001$ vs placebo.

causality. The most frequently reported TEAEs were nausea in the 200-mg group (22 of 155 [14.2%]), nasopharyngitis in the 100-mg group (20 of 158 [12.7%]), and dermatitis atopic in the placebo group (12 of 78 [15.4%]) (Table 2). Median time to cessation of nausea was 7.0 (95% CI, 1.0-14.0) days in the 200-mg group, 2.5 (95% CI, 1.0-7.0) days in the 100-mg group, and 1.0 (95% CI, NE-NE) days in the placebo group.

Serious adverse events were reported for 2 patients in the 200-mg group (1.3%), 5 in the 100-mg group (3.2%), and 1 in

the placebo group (1.3%) (Table 2). Most serious adverse events were considered not related to treatment. There were no treatment-related serious adverse events in the 200-mg group. Serious adverse events that were considered related to treatment were reported for 2 patients in the 100-mg group: 1 patient developed herpangina, and 1 developed pneumonia (in both instances, abrocitinib treatment was discontinued). Two cases of serious adverse events considered related to treatment were reported for 1 patient in the placebo group: 1 case

Figure 3. Peak Pruritus Numerical Rating Scale (PP-NRS) Outcomes



of eczema herpeticum and 1 case of staphylococcal infection (treatment was discontinued, and the patient recovered) (eTable 5 in Supplement 2).

Overall, 5 patients in the 200-mg group (3.2%), 6 in the 100-mg group (3.8%), and 10 in the placebo group (12.8%) discontinued treatment because of adverse events. The most frequently reported adverse events leading to treatment discontinuation were headache (2 [1.3%]) in the 200-mg group, dermatitis atopic (2 [1.3%]) in the 100-mg group, and dermatitis atopic (6 [7.7%]) in the placebo group.

There were no cases of malignant neoplasms or venous thromboembolism in any treatment group. Sudden cardiac death occurred in a woman in her 70s 3 weeks after discontinuation of the 100-mg dose of abrocitinib. This patient had a history of aortic valve sclerosis and untreated hyperten-

sion; the event was considered not related to treatment by the investigator (Table 2).

Serious infections were reported for no patients in the 200-mg group, 3 in the 100-mg group (1.9%), and 1 in the placebo group (1.3%). Herpes zoster TEAEs were reported for 2 patients in the 200-mg group (1.3%) (1 case of 2 adjacent dermatomes and 1 multidermatomal case; no treatment was given, and the cases resolved); no cases were reported in the 100-mg or placebo groups. Eczema herpeticum/Kaposi varicelliform eruption TEAEs were reported for 2 patients in the 100-mg group (1.3%), patients in the 100-mg group (1 patient discontinued treatment), and 1 in the placebo group (1.3%); no cases were reported in the 200-mg group. Other TEAEs of interest reported were acne (9 in the 200-mg group [5.8%], 2 in the 100-mg group [1.3%], and 0 in the placebo group), folliculitis (5 in the 200-mg

Table 2. Summary of Adverse Events

Event	Treatment group, No. (%)		
	Placebo (n = 78)	Abrocitinib	
		100 mg (n = 158)	200 mg (n = 155)
Deaths	0	1 (0.6)	0
Serious adverse events of any cause	1 (1.3)	5 (3.2)	2 (1.3)
Most frequently reported TEAEs of any cause (≥3% in any treatment group)			
Nausea	2 (2.6)	12 (7.6)	22 (14.2)
Nasopharyngitis	5 (6.4)	20 (12.7)	12 (7.7)
Headache	2 (2.6)	9 (5.7)	12 (7.7)
Upper respiratory tract infection	3 (3.8)	14 (8.9)	5 (3.2)
Dermatitis atopic	12 (15.4)	9 (5.7)	6 (3.9)
Acne	0	2 (1.3)	9 (5.8)
Vomiting	1 (1.3)	2 (1.3)	8 (5.2)
Upper abdominal pain	0	2 (1.3)	6 (3.9)
Blood creatine phosphokinase increased	2 (2.6)	3 (1.9)	5 (3.2)
Folliculitis	2 (2.6)	0	5 (3.2)
Thrombocytopenia	0	0	5 (3.2)

Abbreviation: TEAE, treatment-emergent adverse event.

group [3.2%], 0 in the 100-mg group, and 2 in the placebo group [2.6%]), vomiting (8 in the 200-mg group [5.2%], 2 in the 100-mg group [1.3%], and 1 in the placebo group [1.3%]), and upper abdominal pain (6 in the 200-mg group [3.9%], 2 in the 100-mg group [1.3%], and 0 in the placebo group) (Table 2).

Dose-related numeric decreases in median platelet counts were observed in patients treated with abrocitinib. A nadir in median platelet count was observed at week 4, with decreases of 26% in the 200-mg group, 19% in the 100-mg group, and less than 1% in the placebo group. Platelet counts returned toward baseline values thereafter despite continuation of treatment (eFigure 4 in Supplement 2). Most patients maintained platelet counts within the reference range; however, 2 patients required monitoring because of platelet counts of less than $75 \times 10^3/\mu\text{L}$ (to convert to $\times 10^9/\text{L}$, multiply by 0.001). Thrombocytopenia (assessed with laboratory values; 5 [3.2%]) and decreased platelet count (assessed objectively; 2 [1.3%]) TEAEs were reported in the 200-mg group; no events were reported in the 100-mg or placebo groups. The 2 patients with mild reductions in platelet counts recovered with continued treatment. One patient in the 200-mg group discontinued treatment for 8 days because of mild thrombocytopenia (approximately $83 \times 10^3/\mu\text{L}$); the patient recovered, and abrocitinib treatment was reinitiated without additional reports of thrombocytopenia. There were no reports of bleeding disorders in any treatment group.

There were no clinically significant changes in hemoglobin levels or neutrophil or lymphocyte counts. There were dose-related increases of approximately 10% in high- and low-density lipoprotein levels for both abrocitinib doses compared with placebo. Increases in creatinine kinase levels also occurred in the 200-mg and 100-mg groups. All other observed changes in clinical laboratory values, electrocardiographic measurements, and vital signs were not clinically meaningful.

Patient-Reported Outcomes

From weeks 2 to 12, adult (≥ 18 years) and adolescent (< 18 years) patients reported improvement in their quality of life, with greater improvements in DLQI (week 2, -7.9 [95% CI, -8.8 to -7.1] in the 200-mg group, -5.6 [95% CI, -6.5 to -4.8] in the 100-mg group, and -1.6 [95% CI, -2.8 to -0.4] in the placebo group; week 12, -9.8 [95% CI, -10.7 to -8.8] in the 200-mg group, -8.3 [95% CI, -9.3 to -7.3] in the 100-mg group, and -3.9 [95% CI, -5.3 to -2.4] in the placebo group) and CDLQI (week 2, -7.1 [95% CI, -9.6 to -4.6] in the 200-mg group, -3.3 [95% CI, -5.8 to -0.9] in the 100-mg group, and -2.4 [95% CI, -5.8 to 1.1] in the placebo group; week 12, -9.7 [95% CI, -12.1 to -7.4] in the 200-mg group, -4.8 [95% CI, -7.2 to -2.5] in the 100-mg group, and -2.7 [95% CI, -6.1 to 0.8] in the placebo group) scores for both abrocitinib doses compared with placebo (eTable 1 and eFigure 5A-B in Supplement 2). From weeks 2 to 12, abrocitinib-treated patients reported greater improvements in AD severity than placebo-treated patients, measured by Patient-Oriented Eczema Measure (week 2, -7.5 [95% CI, -8.4 to -6.6] in the 200-mg group, -5.2 [95% CI, -6.1 to -4.3] in the 100-mg group, and -0.6 [95% CI, -2.0 to 0.7] in the placebo group; week 12, -11.0 [95% CI, -12.1 to -9.8] in the 200-mg group, -8.7 [95% CI, -9.9 to -7.5] in the 100-mg group, and -3.6 [95% CI, -5.3 to -1.9] in the placebo group) and Patient Global Assessment (week 2, -1.0 [95% CI, -1.1 to -0.9] in the 200-mg group, -0.6 [95% CI, -0.7 to -0.5] in the 100-mg group, and 0.0 [95% CI, -0.2 to 0.1] in the placebo group; week 12, -1.4 [95% CI, -1.6 to -1.2] in the 200-mg group, -1.0 [95% CI, -1.2 to -0.8] in the 100-mg group, and -0.4 [95% CI, -0.7 to -0.1] in the placebo group) (eTable 1 and eFigure 5C-D in Supplement 2), and improvement in anxiety (week 2, -1.3 [95% CI, -1.7 to -0.9] in the 200-mg group, -1.1 [95% CI, -1.5 to -0.7] in the 100-mg group, and -0.3 [95% CI, -0.8 to 0.3] in the placebo group; week 12, -1.7 [95% CI, -2.2 to -1.2] in the 200-mg group, -1.6 [95% CI, -2.1 to -1.1] in the 100-mg group, and -0.6

[95% CI, -1.3 to 0.2] in the placebo group) and depression (week 2, -0.9 [95% CI, -1.3 to -0.6] in the 200-mg group, -0.8 [95% CI, -1.2 to -0.4] in the 100-mg group, and 0.9 [95% CI, 0.3 to 1.4] in the placebo group; week 12, -1.4 [95% CI, -1.8 to -1.0] in the 200-mg group, -1.0 [95% CI, -1.5 to -0.6] in the 100-mg group, and 0.3 [95% CI, -0.3 to 0.9] in the placebo group) measured with the Hospital Anxiety and Depression Scale (eTable 1 and eFigure 5E-F in Supplement 2).

Discussion

Oral abrocitinib in a 200-mg or a 100-mg dose significantly improved AD signs and symptoms compared with placebo in adolescents and adults with moderate-to-severe AD. Similar to the JADE MONO-1 study, IGA and EASI-75 responses were observed as early as week 2 of treatment and were sustained until week 12. Furthermore, similar IGA and EASI-75 responses were observed in analyses for patients younger than 18 years or 18 years or older.

Abrocitinib was well tolerated in this study; the incidences of serious adverse events, adverse events leading to discontinuation, and serious infections were low in the abrocitinib groups compared with the placebo group. Nausea was transient and resulted in treatment discontinuation in 1 patient in the 200-mg group. The incidences of herpes zoster and eczema herpeticum in patients treated with abrocitinib were also low and comparable with those of the placebo group. There were no significant clinical changes in hemoglobin level or neutrophil or lymphocyte counts, consistent with the selective inhibition of JAK1 vs JAK2 for abrocitinib. However, dose-related decreases in median platelet counts were observed at week 4. Platelet count stabilized by week 12 of treatment without clinical sequelae or treatment cessation. Most patients had platelet counts within the reference range throughout the study, but patients with thrombocytopenia, coagulopathy, or platelet dysfunction were excluded from the study. The mechanism that leads to changes in platelet count with abrocitinib treatment is not known. However, it could be a pharmacologic effect of abrocitinib, potentially mediated by the inhibition of JAK1 and downstream inhibition of thrombopoietin production or by the inhibition of Ashwell-Morrell receptors and downstream effects on platelet production.^{32,33}

Pruritus is one of the most bothersome symptoms of AD.^{9,34} In this study, abrocitinib reduced the severity of pruritus compared with placebo within 24 hours after treatment initiation and through week 12. This reduction could explain

the substantial quality-of-life benefits observed in this study. Abrocitinib may mediate this effect through various mechanisms, including relief of inflammation and/or direct inhibition of neuronal JAK1 signaling of pruritogenic cytokines.^{17,35}

The results of the JADE MONO-1 and JADE MONO-2 studies followed similar trends. In both studies, higher proportions of abrocitinib-treated than placebo-treated patients achieved IGA and/or EASI-75 responses at week 12. Abrocitinib was well tolerated, with a low incidence of serious adverse events, similar to placebo. However, compared with the JADE MONO-1 study, the JADE MONO-2 study included a greater proportion of Asian patients (15.0% vs 33.0%, respectively), who have been reported to have different subsets of helper T cell-driven inflammatory activity compared with patients of European descent.³⁶ Together, the results of both trials support the efficacy and safety profile of abrocitinib in a broad range of patients, possibly related to the inhibition of a range of AD-associated cytokines. Comparisons of efficacy and safety results between abrocitinib and dupilumab are complicated by differences in administration route, treatment period, efficacy end point definitions, analysis of efficacy end points, and patient inclusion criteria. However, the efficacy of abrocitinib appears at least comparable to that of dupilumab in a broadly similar patient population.

Limitations

This study was limited by the short duration of the treatment and follow-up periods, which did not address the long-term efficacy and safety of abrocitinib. More patients might have achieved IGA and/or EASI-75 responses with longer treatment. The adolescent and nonwhite patient populations of the study were small, limiting the applicability of abrocitinib in these patient populations. In addition, this study excluded patients with platelet dysfunction, limiting the applicability of these results in this patient population.

Conclusions

Once-daily oral abrocitinib, 200 mg or 100 mg, was well tolerated and significantly improved signs and symptoms of AD compared with placebo in adolescent and adult patients with moderate-to-severe disease. Future studies and analyses should focus on the long-term efficacy and safety of abrocitinib in patients with moderate-to-severe AD and in adolescents and nonwhite patients and explore the use of abrocitinib in combination with topical therapies.

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Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Chan, Feeney, Biswas, DiBonaventura, Rojo.

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Statistical analysis: Chan, Biswas.

Administrative, technical, or material support:

Feeney, Biswas, Valdez, DiBonaventura, Nduka. **Supervision:** Thyssen, Chan, Feeney.

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