Efficacy and Safety of Abrocitinib in Patients With Moderate-to-Severe Atopic Dermatitis: Results From the Phase 3 JADE MONO-1 Study

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BACKGROUND

- Janus kinase 1 (JAK1) is a cytoplasmic tyrosine kinase that mediates signaling pathways activated by various cytokines[1,2]
- Various cytokine pathways relevant to the pathophysiology of atopic dermatitis (AD) signal via JAK1, including interleukin (IL)-2, IL-4, IL-13, IL-22, IL-31, and thymic stromal lymphopoietin, thereby mediating type 2 helper T-cell differentiation and itch through downstream effects[1,2]
- Abrocitinib is an oral once-daily JAK1 selective inhibitor under investigation for the treatment of AD
  - Monotherapy with once-daily abrocitinib 200 mg or 100 mg was effective with an acceptable safety profile in a dose-ranging phase 2b study in adults with moderate-to-severe AD[3]

OBJECTIVE

- To evaluate the efficacy and safety of once-daily, oral abrocitinib (200 mg or 100 mg) versus placebo in adolescent and adult patients with moderate-to-severe AD in JADE MONO-1 (NCT03349060), a randomized, placebo-controlled, phase 3 trial

METHODS

Study Design and Endpoints

- JADE MONO-1 was a multicenter, international, randomized, double-blind, placebo-controlled, monotherapy, phase 3 study
- Patients aged ≥12 years with moderate-to-severe AD (Investigator's Global Assessment [IGA] ≥3; Eczema Area and Severity Index [EASI] score ≥16; affected percentage of body surface area ≥10, and Peak Pruritus Numerical Rating Scale [PP-NRS; used with permission of Regeneron Pharmaceuticals, Inc. and Sanofi] score ≥4) were randomly assigned (2:2:1) to receive once-daily oral abrocitinib 200 mg, abrocitinib 100 mg, or placebo for 12 weeks

Key Assessments

- Coprimary endpoints
  - Proportion of patients achieving IGA response (clear [0] or almost clear [1] with ≥2-grade improvement from baseline) at week 12
  - Proportion of patients achieving EASI ≥75% improvement from baseline (EASI-75) at week 12
- Key secondary endpoints
  - Proportion of patients achieving PP-NRS response (≥4-point improvement from baseline) at weeks 2, 4, and 12
- Other secondary endpoints (not multiplicity controlled)
  - Proportion of patients achieving IGA response at all other scheduled time points
  - Proportion of patients achieving EASI-75 at all other scheduled time points
  - Proportion of patients achieving EASI ≥90% improvement from baseline (EASI-90) at all scheduled time points
  - Proportion of patients with PP-NRS response at all other scheduled time points
  - Time to PP-NRS response
- Safety was assessed via adverse event (AE) and laboratory monitoring

Statistical analysis

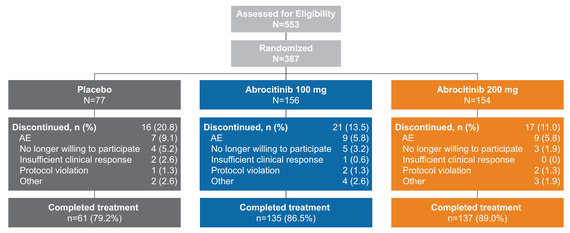
- Coprimary, key secondary, and other binary endpoints were analyzed using the Cochran-Mantel-Haenszel test, adjusted for randomization strata (baseline disease severity and age group)
- All continuous endpoints were analyzed using a mixed-effect model with repeated measures based on all observed data. The model included factors (fixed effects) for treatment group, randomization strata, visit, treatment-by-visit interaction, and relevant baseline value
- Safety data and clinical laboratory parameters were summarized with descriptive statistics

RESULTS

Patient Disposition, Demographics, and Baseline Disease Characteristics

- Most patients in all treatment arms completed the study (**Figure 1**)
- Demographics and baseline disease characteristics were balanced across treatment arms (**Table 1**)

Figure 1. Patient Disposition



AE, adverse event.

Table 1. Demographics and Baseline Disease Characteristics

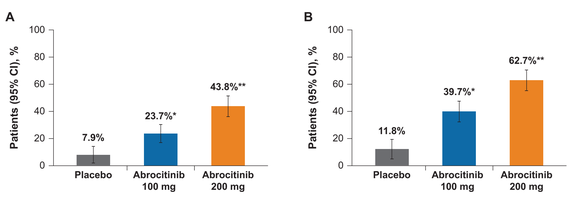
Characteristic	Placebo N=77	Abrocitinib 100 mg N=156	Abrocitinib 200 mg N=154	Total N=387
Age, mean (SD), y	31.5 (14.4)	32.6 (15.4)	33.0 (17.4)	32.5 (16.0)
Age group, n (%)				
<18 y	17 (22.1)	34 (21.8)	33 (21.4)	84 (21.7)
≥18 y	60 (77.9)	122 (78.2)	121 (78.6)	303 (78.3)
Male, n (%)	49 (63.6)	90 (57.7)	81 (52.6)	220 (56.8)
White, n (%)	62 (80.5)	113 (72.4)	104 (67.5)	279 (72.1)
Disease duration, median (range), y	18.8 (2-66)	21.3 (1-69)	18.9 (1-65)	19.8 (1-69)
Prior medication for AD,[a] n (%)	41 (53.2)	78 (50.0)	68 (44.2)	187 (48.3)
IGA, n (%)				
Moderate (3)	46 (59.7)	92 (59.0)	91 (59.1)	229 (59.2)
Severe (4)	31 (40.3)	64 (41.0)	63 (40.9)	158 (40.8)
EASI, mean (SD)	28.7 (12.5)	31.3 (13.6)	30.6 (14.1)	30.5 (13.6)
PP-NRS, mean (SD)	7.0 (1.8)	6.9 (2.0)	7.1 (1.9)	7.0 (1.9)

AD, atopic dermatitis; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; PP-NRS, Peak Pruritus Numerical Rating Scale.
[a]Included mycophenolate mofetil, methotrexate, azathioprine, corticosteroids, ciclosporin, and dupilumab.

Efficacy

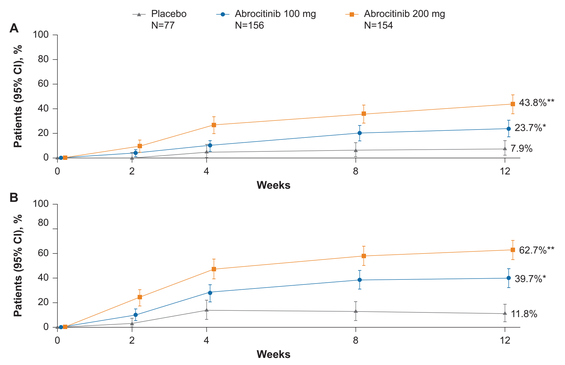
- At week 12, significantly more abrocitinib-treated (200 mg and 100 mg) than placebo-treated patients achieved IGA response (**Figure 2A**)
  - Differences in IGA response rates compared with placebo for abrocitinib 200 mg and 100 mg were 36.0% (95% CI, 26.2–45.7; *P*<0.0001) and 15.8% (95% CI, 6.8–24.8; *P*<0.005), respectively
- At week 12, significantly more abrocitinib-treated (200 mg and 100 mg) than placebo-treated patients achieved EASI-75 response (**Figure 2B**)
  - Differences in EASI-75 response rates compared with placebo for abrocitinib 200 mg and 100 mg were 51.0% (95% CI, 40.5–61.5; *P*<0.0001) and 27.9% (95% CI, 17.4–38.3; *P*<0.0001), respectively
- Proportions of patients achieving IGA or EASI-75 responses were higher with abrocitinib treatment at weeks 2, 4, and 8 than with placebo and increased through week 12 (**Figure 3**)

Figure 2. Proportion of Patients Achieving (A) IGA or (B) EASI-75 at Week 12



EASI-75, ≥75% improvement in Eczema Area and Severity Index; IGA, Investigator's Global Assessment. IGA response defined as clear [0] or almost clear [1] with ≥2-grade improvement from baseline.
*P<0.01, **P<0.0001 versus placebo.

Figure 3. Proportion of Patients Achieving (A) IGA or (B) EASI-75 Responses



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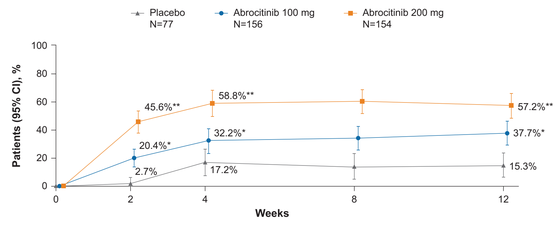
*P<0.01, **P<0.0001 versus placebo.

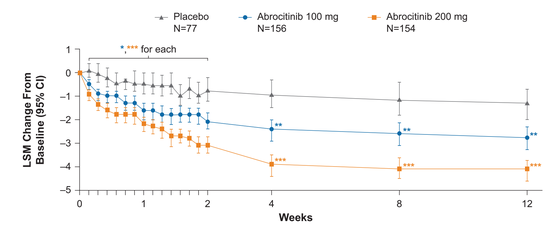
- Proportions of patients achieving EASI-90 response increased from week 2 to week 12 for both abrocitinib doses compared with placebo; EASI-90 responses at week 12 were 38.6%, 18.6%, and 5.3% at week 12 for the 200-mg, 100-mg, and placebo groups, respectively
- Proportion of patients achieving PP-NRS response increased from week 2 to week 12 for both abrocitinib doses, with significant differences from placebo at weeks 2, 4, 8, and 12 (**Figure 4**)
  - Median times (95% CI) to first achievement of PP-NRS response from Kaplan-Meier analysis were 14.0 days (11.0-29.0), 84.0 days (56.0-not evaluable [NE]), and 92.0 days (85.0-NE) in the 200-mg, 100-mg, and placebo groups, respectively
- PP-NRS scores decreased from baseline to week 12 for both abrocitinib doses compared with placebo, with statistically significant reductions observed within 1 day of the first dose of treatment (**Figure 5**)

Figure 4. Proportion of Patients Achieving PP-NRS Response (≥4-point improvement from baseline)



PP-NRS, Peak Pruritus Numerical Rating Scale.
Estimated number of responders and response rates were obtained from a multiple-imputation procedure accounting for any intermittent missing data that were not already handled by nonresponder imputation.
*P<0.001, **P<0.0001 versus placebo.

Figure 5. PP-NRS Change From Baseline



LSM, least squares mean; PP-NRS, Peak Pruritus Numerical Rating Scale.
*P<0.05, **P<0.001, ***P<0.0001 versus placebo.

Safety

- The most frequently reported treatment-emergent AEs were nausea and nasopharyngitis in abrocitinib-treated patients and dermatitis atopic in placebo-treated patients (**Table 2**)
- A higher proportion of patients in the placebo group discontinued treatment because of AEs than patients in either abrocitinib group (**Table 2**)
- The incidences of herpes zoster and eczema herpeticum were low with abrocitinib treatment compared with placebo (**Table 2**)
- There were no deaths, cases of venous thromboembolism, malignancy, or major adverse cardiovascular events
- Clinical laboratory evaluations:
  - Hemoglobin, neutrophils, and lymphocytes showed no clinically significant changes
  - Platelet counts reached a nadir at week 4 and trended toward baseline thereafter despite continued therapy
  - Dose-related changes in lipid levels were observed (~10% increase in low-density lipoprotein and ~20% increase in high-density lipoprotein)

Table 2. Summary of Adverse Events

n (%)	Placebo N=77	Abrocitinib 100 mg N=156	Abrocitinib 200 mg N=154
TEAEs	44 (57.1)	108 (69.2)	120 (77.9)
Serious AEs	3 (3.9)	5 (3.2)	5 (3.2)
Discontinuation because of AEs	7 (9.1)	9 (5.8)	9 5.8)
Deaths	0	0	0
Venous thromboembolism[a]	0	0	0
Herpes zoster	0	1 (0.6)	1 (0.6)
Eczema herpeticum	0	1 (0.6)	0
TEAEs in ≥5.0% of patients in any group			
Nausea	2 (2.6)	14 (9.0)	31 (20.1)
Nasopharyngitis	8 (10.4)	23 (14.7)	18 (11.7)
Headache	2 (2.6)	12 (7.7)	15 (9.7)
Upper respiratory tract infection	5 (6.5)	11 (7.1)	11 (7.1)
Dermatitis atopic	13 (16.9)	22 (14.1)	8 (5.2)

AE, adverse event; TEAE, treatment-emergent adverse event.
[a]Study not designed to assess people at higher risk for venous thromboembolism.

CONCLUSIONS

- Abrocitinib 200 mg or 100 mg once daily significantly improved signs and symptoms of moderate-to-severe AD compared with placebo in adolescent and adult patients
- Abrocitinib was well tolerated and showed an acceptable short-term safety profile
- Abrocitinib represents a novel oral therapy for adult and adolescent patients with moderate-to-severe AD

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