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

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BACKGROUND

- Treatment options are limited for patients with moderate-to-severe atopic dermatitis (AD) unresponsive to topical agents
- Dupilumab, an anti-interleukin 4 receptor α monoclonal antibody, is a subcutaneous treatment approved for patients with AD who are candidates for systemic therapy[1]
- Abrocitinib, an oral once-daily selective Janus kinase 1 inhibitor[2] under investigation for the treatment of moderate-to-severe AD, has brought about substantial improvement in AD signs and symptoms, including rapid itch relief[3,4]
- We report the results from JADE COMPARE (NCT03720470), a phase 3 clinical trial conducted to investigate the efficacy of once-daily abrocitinib 200 mg or 100 mg compared with placebo and dupilumab in adults with moderate-to-severe AD who were receiving standard medicated topical therapy

OBJECTIVE

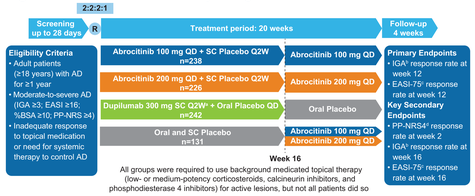
- The primary objective was to evaluate the efficacy of once-daily abrocitinib (200 mg or 100 mg) compared with placebo in treating patients with AD who were receiving medicated topical therapy
- Key secondary objectives were to compare itch response after use of abrocitinib and after use of dupilumab at 2 weeks and to estimate the proportion of patients in the 3 active treatment arms whose AD signs improved

METHODS

Study Overview

- JADE COMPARE was a multicenter, randomized, double-blind, double-dummy, placebo-controlled phase 3 trial (**Figure 1**)

Figure 1. JADE COMPARE Study Design



All groups were required to use background medicated topical therapy (low- or medium-potency corticosteroids, calcineurin inhibitors, and phosphodiesterase 4 inhibitors) for active lesions, but not all patients did so

%BSA, percentage of affected body surface area; AD, atopic dermatitis; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; PP-NRS, Peak Pruritus Numerical Rating Scale; QD, once daily; Q2W, every 2 weeks; R, randomization; SC, subcutaneous.

[a]After ≥600-mg SC loading dose of dupilumab.
[b]IGA response defined as clear (0) or almost clear (1) with ≥2-grade improvement from baseline.
[c]EASI-75 response defined as ≥75% improvement from baseline.
[d]PP-NRS4 response defined as ≥4-point improvement in PP-NRS score. The PP-NRS is used with permission of Regeneron Pharmaceuticals, Inc., and Sanofi.

Statistical Analysis

- The familywise type 1 error rate for testing the coprimary and key secondary endpoints was strongly controlled at 5% using a sequential, Bonferroni-based, iterative, multiple-testing procedure
  - Testing of all other secondary endpoints was done at the nominal 5% significance level and was not controlled for multiplicity
- Efficacy was analyzed in the full analysis set, defined as all patients randomly assigned to receive treatment who received ≥1 dose of study medication
- Coprimary, key secondary, and other binary endpoints were analyzed using the Cochran-Mantel-Haenszel test, adjusted by baseline disease severity

RESULTS

Demographics and Baseline Disease Characteristics

- Demographics and baseline disease characteristics were balanced across groups (**Table 1**)

Coprimary and Key Secondary Endpoints: IGA and EASI-75 Responses at Week 12 and Week 16

- A significantly greater proportion of patients in both abrocitinib groups met criteria for Investigator's Global Assessment (IGA) and ≥75% improvement from baseline on the Eczema Area and Severity Index (EASI-75) responses at week 12 (coprimary endpoints) and week 16 (key secondary endpoints) compared with patients in the placebo group (**Figure 2**)

Key Secondary Endpoint: Pruritus (PP-NRS4) Response at Week 2

- A significantly greater proportion of patients in both abrocitinib groups met criteria for ≥4-point improvement in Peak Pruritus Numerical Rating Scale (PP-NRS4) response at week 2 compared with patients in the placebo group (**Figure 3**)
- A significantly greater proportion of patients achieved PP-NRS4 response at week 2 in the abrocitinib 200-mg group compared with patients in the dupilumab group

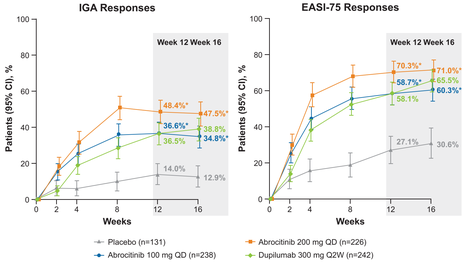
Table 1. Demographics and Baseline Disease Characteristics

	Placebo n=131	Abrocitinib 100 mg QD n=238	Abrocitinib 200 mg QD n=226	Dupilumab 300 mg Q2W n=242
Age, mean (SD), y	37.4 (15.2)	37.3 (14.8)	38.8 (14.5)	37.1 (14.6)
Female, n (%)	54 (41.2)	118 (49.6)	122 (54.0)	134 (55.4)
Race, n (%) White Black Asian Other	87 (66.4) 6 (4.6) 31 (23.7) 7 (5.4)	182 (76.5) 6 (2.5) 48 (20.2) 2 (0.8)	161 (71.2) 9 (4.0) 53 (23.5) 3 (1.2)	176 (72.7) 14 (5.8) 46 (19.0) 6 (2.4)
Duration of AD, mean (SD), y	21.4 (14.4)	22.7 (16.3)	23.4 (15.6)	22.8 (14.8)
IGA,[a] n (%) Moderate (3) Severe (4)	88 (67.2) 43 (32.8)	153 (64.3) 85 (35.7)	138 (61.1) 88 (38.9)	162 (66.9) 80 (33.1)
EASI,[b] mean (SD)	31.0 (12.6)	30.3 (13.5)	32.1 (13.1)	30.4 (12.0)
%BSA, mean (SD)	48.9 (24.9)	48.1 (23.1)	50.8 (23.0)	46.5 (22.1)
PP-NRS,[c] mean (SD)	7.1 (1.8)	7.1 (1.7)	7.6 (1.5)	7.3 (1.7)

%BSA, percentage of affected body surface area; AD, atopic dermatitis; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; PP-NRS, Peak Pruritus Numerical Rating Scale; Q2W, every 2 weeks; QD, once daily.

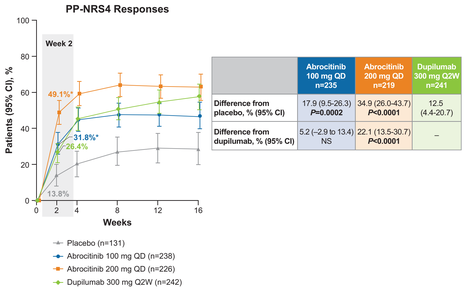
[a]IGA ranges from clear (0) to severe (4).
[b]EASI ranges from 0 to 72, with higher scores indicating more severe disease.
[c]PP-NRS scores represent maximum itch severity in the previous 24 hours. Scores range from 0 to 10, with higher scores representing more severe itch.

Figure 2. Coprimary and Key Secondary Endpoints: IGA and EASI-75 Responses at Week 12 and Week 16



EASI-75, ≥75% improvement from baseline on Eczema Area and Severity Index; IGA, Investigator's Global Assessment.
*P<0.0001 for abrocitinib 200 mg and 100 mg compared with placebo.

Figure 3. Key Secondary Endpoint: PP-NRS4 Response at Week 2



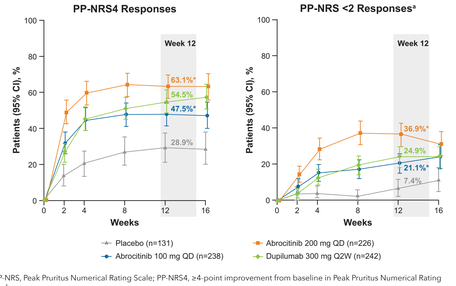
	Abrocitinib 100 mg QD n=235	Abrocitinib 200 mg QD n=219	Dupilumab 300 mg Q2W n=241
Difference from placebo, % (95% CI)	17.9 (9.5-26.3) *P*<0.0002	34.9 (26.0-43.7) *P*<0.0001	12.5 (4.4-20.7)
Difference from dupilumab, % (95% CI)	5.2 (−2.9 to 13.4) NS	22.1 (13.5-30.7) *P*<0.0001	–

NS, not significant; PP-NRS4, ≥4-point improvement in Peak Pruritus Numerical Rating Scale score; Q2W, every 2 weeks; QD, once daily. Dash signifies "not assessed."
*P<0.0001 for abrocitinib 200 mg versus placebo and dupilumab; *P*=0.0002 for abrocitinib 100 mg versus placebo.

Additional PP-NRS Endpoints

- A significantly greater proportion of patients achieved PP-NRS4 and PP-NRS <2 responses at week 12 in the abrocitinib 200-mg and 100-mg groups than those given placebo (**Figure 4**)

Figure 4. PP-NRS4 and PP-NRS <2 Response Rates at Week 12

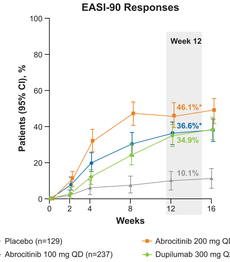


PP-NRS, Peak Pruritus Numerical Rating Scale; PP-NRS4, ≥4-point improvement from baseline in Peak Pruritus Numerical Rating Scale score.
[a]Post hoc analysis; represents almost complete resolution of itch.
*P<0.0001 for abrocitinib 200 mg and *P*=0.0009 for abrocitinib 100 mg compared with placebo. Conclusion of statistical significance was not controlled for multiplicity.

Depth of Response: ≥90% Improvement From Baseline in EASI Responses at Week 12

- A significantly greater proportion of patients achieved ≥90% improvement from baseline in EASI (EASI-90) responses at week 12 in the abrocitinib 200-mg and 100-mg groups compared with the placebo group (**Figure 5**)

Figure 5. Depth of Response: EASI-90 Responses at Week 12



EASI-90, ≥90% improvement from baseline in Eczema Area and Severity Index; Q2W, every 2 weeks; QD, once daily.
*P<0.0001 for abrocitinib 200 mg and 100 mg compared with placebo. Conclusion of statistical significance was not controlled for multiplicity.

Safety Summary

- Few patients had serious or severe adverse events (**Table 2**)
- Nausea and acne occurred more frequently with abrocitinib, and conjunctivitis occurred more frequently with dupilumab

Table 2. Safety Summary

	Placebo n=131	Abrocitinib 100 mg QD n=238	Abrocitinib 200 mg QD n=226	Dupilumab 300 mg Q2W n=242
Patients who had ≥1 AE, n (%)	70 (53.4)	121 (50.8)	140 (61.9)	121 (50.0)
Serious AEs	5 (3.8)	6 (2.5)	2 (0.9)	2 (0.8)
Severe AEs	3 (2.3)	5 (2.1)	4 (1.8)	2 (0.8)
AEs leading to study discontinuation	5 (3.8)	6 (2.5)	10 (4.4)	8 (3.3)
AEs reported for ≥5% of patients in any group, n (%)				
Nausea	2 (1.5)	10 (4.2)	25 (11.1)	7 (2.9)
Conjunctivitis	3 (2.3)	2 (0.8)	3 (1.3)	15 (6.2)
Nasopharyngitis	9 (6.9)	22 (9.2)	15 (6.6)	23 (9.5)
Upper respiratory tract infection	6 (4.6)	12 (5.0)	9 (4.0)	9 (3.7)
Headache	6 (4.6)	10 (4.2)	15 (6.6)	13 (5.4)
Acne	0	7 (2.9)	15 (6.6)	3 (1.2)
Herpes zoster[a]	0	2 (0.8)	4 (1.8)	0

AE, adverse event; Q2W, every 2 weeks; QD, once daily.
[a]AE did not reach threshold of ≥5% in any group but has been included because of clinical interest in the incidence of AD.

CONCLUSIONS

- At week 12, the 200-mg and 100-mg once-daily doses of abrocitinib were significantly more efficacious than placebo at relieving AD signs and symptoms in patients with moderate-to-severe AD who were receiving medicated topical therapy
- Itch response was more rapid with abrocitinib 200 mg than with dupilumab
  - The proportion of patients who experienced itch response at week 2 was significantly greater with abrocitinib 200 mg than with placebo or with dupilumab
  - Itch response with abrocitinib 100 mg was significantly higher at week 2 than with placebo and was comparable to that of dupilumab
- The rate of adverse events was higher with abrocitinib 200 mg than with placebo or dupilumab, whereas the rate with abrocitinib 100 mg was similar to that of dupilumab
  - However, few patients in any treatment group experienced serious or severe adverse events, and the adverse events that most frequently occurred with abrocitinib (nausea, acne) were mild to moderate and transient

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