Examining the Relationships Between Abrocitinib Monotherapy, Pruritus Severity, and Skin Clearance in Patients With Moderate-to-Severe Atopic Dermatitis: Results From JADE MONO-1 and JADE MONO-2

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BACKGROUND

- Atopic dermatitis (AD) is a chronic inflammatory skin disorder characterized by intense pruritus and eczematous lesions[1]
- Pruritus, the hallmark symptom of AD, significantly impacts the quality of life of patients with moderate-to-severe AD[2]; the interrelationships between the severity of pruritus, the severity and extent of clinical signs of AD, and treatment have not been established
- Abrocitinib, an oral once-daily Janus kinase (JAK) 1 selective inhibitor, improved pruritus and skin clearance in patients with moderate-to-severe AD in 2 phase 3 monotherapy trials (JADE MONO-1 [NCT03349060] and JADE MONO-2 [NCT03575871]) and the phase 3 JADE COMPARE (NCT03720470) trial of abrocitinib in combination with background medicated topical therapy[3-5]
- JAK signaling promotes inflammation, and recent evidence suggests JAK signaling may directly transmit itch signals in neurons; thus, JAK inhibition may decrease itch through indirect (decrease in inflammation) and direct mechanisms (inhibiting neuronal itch signals)[6]

OBJECTIVE

- To evaluate, using mediation modeling and pooled data from the JADE MONO-1 and JADE MONO-2 studies, whether the improvement in itch observed in patients treated with abrocitinib occurs via direct or indirect mechanisms

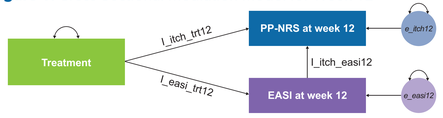
METHODS

- Mediation modeling can be used to assess direct and indirect effects of a treatment on outcomes[7]
- A mediation model was used to explain the mechanism underlying relationships between the predictor (treatment, abrocitinib vs placebo) and the outcome (severity of pruritus, measured using the Peak Pruritus Numerical Rating Scale [PP-NRS], used with permission of Regeneron Pharmaceuticals, Inc., and Sanofi[8]) through the inclusion of other variables (AD skin clearance, measured using the Eczema Area and Severity Index [EASI], which assesses erythema, induration or papulation, excoriation, and lichenification and extent of AD skin involvement[9]) denoted as mediators
- 3 models were considered in this analysis: a cross-sectional mediation model, a longitudinal mediation model, and a pseudo steady state mediation model

Cross-Sectional Mediation Model

- In the cross-sectional mediation model, the interrelationships between variables were assessed separately at weeks 2, 4, 8, and 12 (an example for Week 12 is shown in **Figure 1**)

Figure 1. Cross-Sectional Mediation Model for Week 12



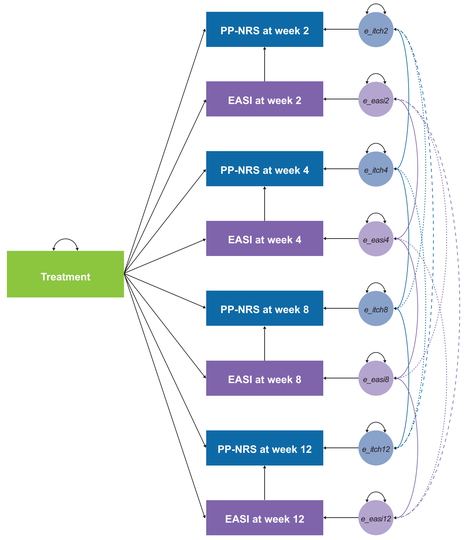
EASI, Eczema Area and Severity Index; PP-NRS, Peak Pruritus Numerical Rating Scale.

Treatment is a binary variable–"abrocitinib" (value of 1) versus "placebo" (value of 0); variables e_itch12, e_easi12 represent error terms; curved 2-headed (black) arrow pointing to the same variable represents variance.

Longitudinal Mediation Model

- In the longitudinal mediation model, the interrelationships between variables were evaluated using data from all weeks simultaneously (**Figure 2**)

Figure 2. Longitudinal Mediation Model



EASI, Eczema Area and Severity Index; PP-NRS, Peak Pruritus Numerical Rating Scale.

Treatment is a binary variable–"abrocitinib" (value of 1) versus "placebo" (value of 0); variables e_itch2, e_itch4, e_itch8, e_itch12 and e_easi2, e_easi4, e_easi8, e_easi12 represent error terms; curved 2-headed (blue and purple) arrows between error terms represent covariances; curved 2-headed (black) arrow pointing to the same variable represents variance.

Pseudo Steady State Model

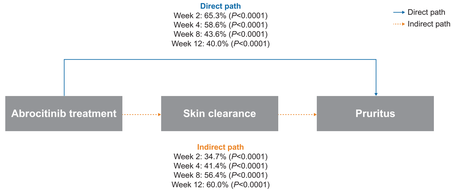
- Based on the cross-sectional and the longitudinal mediation models, a time point at which the model stopped varying (achieving a pseudo steady state) was identified, and a pseudo steady state mediation model was assessed using data starting with that time point

RESULTS

Cross-Sectional Mediation Modeling

- The indirect and direct effects of abrocitinib on pruritus severity estimated by the cross-sectional mediation model are summarized in **Figure 3**

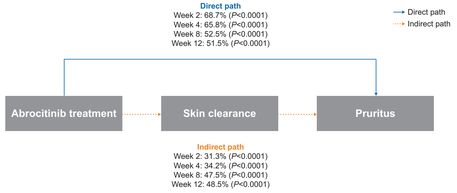
Figure 3. Estimated Direct and Indirect Effects of Abrocitinib on Pruritus Severity (cross-sectional models) at Weeks 2, 4, 8, and 12



Longitudinal Mediation Modeling

- The indirect and direct effects of abrocitinib on pruritus severity estimated by the longitudinal model are summarized in **Figure 4**

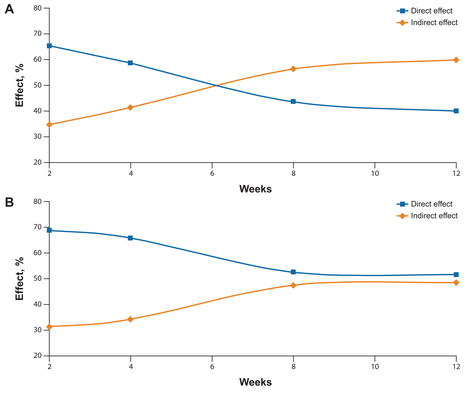
Figure 4. Estimated Direct and Indirect Effects of Abrocitinib on Pruritus Severity (longitudinal model) at Weeks 2, 4, 8, and 12



Pseudo Steady State Mediation Modeling

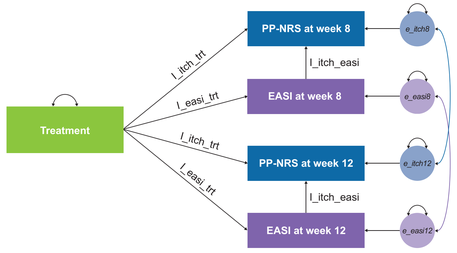
- Cross-sectional and longitudinal models suggest that, starting with week 8, the estimated proportion of the direct and indirect effects stopped varying and achieved a pseudo steady state (**Figures 5A, 5B**)
- The pseudo steady state mediation model assumed that relationships between variables in the model are the same at both time points (weeks 8 and 12), which was done by equating corresponding path coefficients at both time points (**Figure 6**)
- The indirect and direct effects of abrocitinib on pruritus severity estimated by the pseudo steady state mediation model are summarized in **Figure 7**

Figure 5. Estimated Direct and Indirect Effects Over Time for the (A) Cross-Sectional Models and (B) Longitudinal Model



Both models indicate that the period from week 8 to week 12 can be considered a steady state (an equilibrium in which the contributions of direct effects and indirect effect do not appreciably vary with time) for mediation models describing relationships between itch, skin clearance, and treatment.

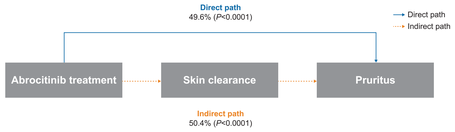
Figure 6. Pseudo Steady State Model



EASI, Eczema Area and Severity Index; PP-NRS, Peak Pruritus Numerical Rating Scale.

Treatment is a binary variable–"abrocitinib" (value of 1) versus "placebo" (value of 0); variables e_itch8, e_itch12 and e_easi8, e_easi12 represent error terms; curved 2-headed (blue and purple) arrows between error terms represent covariances; curved 2-headed (black) arrow pointing to the same variable represents variance.

Figure 7. Estimated Direct and Indirect Effects of Abrocitinib on Pruritus Severity (pseudo steady state model using data from week 8 onward)



CONCLUSIONS

- Both the cross-sectional and the longitudinal mediation models show that effects of abrocitinib on pruritus severity are mainly direct at earlier time points (weeks 2 and 4), achieving a pseudo steady state at week 8, with approximately equal indirect and direct effects at weeks 8 and 12
- The results of the pseudo steady state mediation model show that approximately half the effect of abrocitinib on pruritus severity is indirectly mediated by improvement in AD skin clearance, whereas the remaining half represents the direct effect of abrocitinib on improving pruritus
- These results indicate that abrocitinib has a notable effect on itch independent of its effect on skin clearance

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