Examining the Relationships Among 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: Pruritus, the hallmark symptom of atopic dermatitis (AD), significantly impacts the quality of life of patients with moderate-to-severe AD. However, the interrelationships among 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 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]).

Objectives: To evaluate the interrelationships among treatment, pruritus severity, and skin clearance in AD using mediation modeling and pooled data from the JADE MONO-1 and JADE MONO-2 studies.

Methods: A mediation model was used to explain the mechanism underlying relationships among 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) through the inclusion of other variables (AD skin clearance, measured using the Eczema Area and Severity Index [EASI], which assesses erythema, induration/papulation, excoriation, and lichenification and extent of AD skin involvement) denoted as mediators. Three models were considered in this analysis: a cross-sectional mediation model, a longitudinal mediation model, and a pseudo steady state mediation model. In the cross-sectional mediation model, the interrelationships among variables were assessed separately at weeks 2, 4, 8, and 12. In the longitudinal mediation model, the interrelationships among variables were evaluated using data from all weeks simultaneously. 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: In the cross-sectional mediation model, the indirect effect of abrocitinib on pruritus severity (mediated via skin clearance) ranged from 34.7% to 60.0% (P<0.0001 for weeks 2, 4, 8, and 12) in 704, 576, 581, and 563 patients at weeks 2, 4, 8, and 12, respectively. The direct effect of treatment on pruritus severity ranged from 40.0% to 65.3% (P<0.0001 for weeks 2, 4, 8, and 12). In the longitudinal mediation model, the indirect effect of abrocitinib treatment on pruritus severity ranged from 31.3% to 48.5% (P<0.0001 for weeks 2, 4, 8, and 12) in 383

patients for whom observations were available at all time points. The direct effect ranged from 51.5% to 68.7% (*P*<0.0001 for weeks 2, 4, 8, and 12). The results of the cross-sectional and longitudinal mediation models indicated that a pseudo steady state for the interrelationships was reached at week 8. The pseudo steady state mediation model showed that indirect and direct effects of abrocitinib treatment on pruritus severity were approximately equal and statistically significant (50.4% and 49.6%, respectively; *P*<0.0001 for both; Figure).

Conclusion: Both the longitudinal and the cross-sectional mediation models show that the effect of abrocitinib on pruritus severity is mainly direct at the 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. This indicates that abrocitinib has a notable effect on itch independent from its effect on skin clearance.

Figure. Pseudo Steady State Mediation Model: Direct and Indirect Effects of Abrocitinib on Pruritus Severity