A Phase 2a, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study Evaluating the Mechanism of Action of Abrocitinib Monotherapy for Moderate-to-Severe Atopic Dermatitis (JADE MOA)

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Atopic dermatitis (AD) is a chronic, inflammatory skin disorder characterized by itching and skin lesions, and it often results in deterioration of patient quality of life. Dysregulation of the proinflammatory immune response and skin barrier dysfunction is a key factor underlying the pathogenesis of AD. Skin barrier dysfunction is associated with impaired terminal differentiation that is reflected in reduced expression of differentiation markers, such as filaggrin. Effector immune cells are recruited to sites of aberrant inflammation in response to proinflammatory signals released by injured keratinocytes. In the acute phase, type 2 helper T cells (Th) Th2, Th17, and Th22 predominate. Increased Th1 activation, along with Th2 and Th22 inflammation characterizes the chronic phase of the disease.

The Janus kinase (JAK) signaling pathway plays a key role in mediating the underlying pathologic immune response in patients with AD. Specifically, the JAK-STAT pathway plays a major role in upregulating the expression of proinflammatory cytokines, Th2 cell differentiation, and proliferation, and the mediation of inflammatory responses in AD. This release of type 2 cytokines has a profound role in the development of chronic itch, a key symptom of AD. Abrocitinib is a selective JAK1 inhibitor under investigation as an oral once-daily treatment for moderate-to-severe AD. JADE MOA (NCT03915496) is a randomized, double-blind, placebo-controlled, parallel-group, multicenter, phase 2a study designed to investigate the mechanism of action of abrocitinib by correlating efficacy outcomes with changes from baseline in key skin and blood biomarkers in adults (≥18 years of age) with moderate-to-severe AD.
Objectives and Study Design

Objectives

Primary
- To evaluate changes from baseline to week 12 in AD biomarkers in lesional and nonlesional skin

Key Secondary
- To assess changes from baseline to week 12 in
  - Gene expression
  - Markers of cellular inflammation
  - Markers of epidermal hyperplasia
  - Clinical measures of AD and pruritus and correlation with immunohistochemistry and biomarkers

Study Design
- The study duration was 20 weeks and consisted of 3 periods
  - A 4-week screening period
  - A 12-week blinded, randomized treatment period in which eligible patients were assigned to receive once-daily oral abrocitinib 200 mg, abrocitinib 100 mg, or placebo
  - A 4-week safety follow-up period

Eligibility Criteria
- Adults (≥18 years) with AD ≥1 year
- Moderate-to-severe AD (IGA score ≥3; EASI score ≥16; %BSA ≥10; PP-NRS score ≥4)
- Recent history of inadequate response to medicated topical therapy or need for systemic therapy to control AD
- No history of thrombocytopenia, coagulopathy, or platelet dysfunction

Primary endpoint: changes from baseline in AD skin biomarkers, including biomarkers for general inflammation (MMP12), hyperplasia (K16), Th2 immune response (CCL17, CCL18, CCL26), and Th22 immune response (S100A8, S100A9, S100A12), in lesional and nonlesional skin

Secondary endpoints: change from baseline in gene expression, cellular (T-cell and dendritic cell) inflammation markers, epidermal hyperplasia markers (thickness, K16, K67), blood biomarkers (OLINK proteomic microassay for inflammation and immune response in serum), T-cell lymphocyte subset populations in blood using flow cytometry; correlation of PP-NRS response (≥4-point improvement) and change in immunohistochemistry and genetic markers in lesional skin

%BSA, percentage of body surface area affected; EASI, Eczema Area and Severity Index; hs-CRP, high-sensitivity C-reactive protein; IGA, Investigator’s Global Assessment; IL, interleukin; NTIS, Night Time Itch Scale; PP-NRS, Peak Pruritus Numerical Rating Scale; R, randomization.
The PP-NRS is used with permission of Regeneron Pharmaceuticals, Inc., and Sanofi.
Assessment and Follow-Up

• IGA and EASI assessments will be conducted during the screening period, at baseline, every 2 weeks (Q2W) through week 4, and every 4 weeks (Q4W) thereafter until the end of the study (EOS)

• The patient-reported outcomes (PROs), PP-NRS, NTIS, will be assessed during the screening period, at baseline, daily through day 15, and at weeks 4, 8, 12, and 16

• Lesional skin biopsy (punch biopsy) is required at baseline/day 1 (week 0), day 29 (week 4), and day 85 (week 12), with an optional lesional skin biopsy at day 15 (week 2)

• Nonlesional skin biopsy is required at baseline/day 1 (week 0), with an optional nonlesional skin biopsy at day 85 (week 12)

• Adverse events will be monitored throughout the study

Status

• The study is enrolling or planning to enroll at sites in Canada and the United States. Enrolling countries are shown in yellow.