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693 - Efficacy and safety of orismilast, a potent PDE4B/D inhibitor, in adults with moderate-to-severe atopic dermatitis: a phase 2b randomized, double-blind, placebo-controlled clinical trial (ADESOS)

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Introduction/Background

Orismilast is a potent selective phosphodiesterase 4 (PDE4)-B and -D inhibitor, showing significant efficacy in a Phase 2b psoriasis study.[1,2] PDE4-B and PDE4-D isoforms are over-expressed in the skin of patients with atopic dermatitis (AD), compared to healthy individuals.[3] Enhanced PDE4 activity has also been observed in peripheral blood leukocytes in AD. Orismilast inhibits PDE4-B/D isoforms up to 39 times more potently than apremilast,[1] leading to potent suppression of Th1, Th17, and Th2 effector cytokines.[1]

Objectives

To evaluate efficacy and safety of orismilast versus placebo in adults with moderate-to-severe AD.

Methods

ADESOS is a 16-week, phase 2b, double-blinded, placebo-controlled, dose-finding study assessing efficacy and safety of orismilast in adults with moderate-to-severe AD. Patients were randomized (1:1:1:1) to orismilast 20, 30, 40 mg, or placebo, twice daily. Randomized and dosed patients were included in the Intent-to-Treat Population. Missing data were handled using Multiple Imputation (MI) for the analysis of primary and secondary efficacy endpoints.

Results

Baseline demographics and disease characteristics were generally balanced across groups for the 233 dosed patients. Significantly more patients achieved IGA0/1 responses at Week 16 in orismilast 20 (n=58), 30 (n=61), and 40 mg (n=59) groups, compared to placebo (n=55) (26.3%, 24.3%, 30.9%, and 9.5%, respectively; all p-values <0.05). All active arms demonstrated a significant ≥4-point reduction in itch NRS at Week 2, compared to placebo (p <0.05). Similarly, Patient Global Impression of Change of "much or very much improved" was significant in active arms compared to placebo at Week 16. Mean percentage changes in EASI at Week 16 were -55.1%, - 52.2%, -61.4%, and -50.4%, in orismilast 20, 30, 40 mg and placebo groups, respectively (p>0,05). Mean EASI at baseline was 23, the least severe reported in Phase 2b/3 studies in moderate-to-severe AD.[4] In a subgroup analysis of patients with baseline EASI >21 separation from placebo was increased in the 20 and 40 mg arms, as patients on placebo achieving EASI75 and EASI90 were reduced by 50% and 67%, for the severe population versus the full population.

At Week 16, percentages of patients experiencing any Treatment Emergent Adverse Event (TEAE) were orismilast 20 mg, 76%; 30 mg, 79%; 40 mg, 86%; and placebo, 64%. Infection rates were numerically lower in the orismilast groups compared to placebo groups. The most common TEAEs were diarrhea, nausea, and headache, mainly seen within the first month, mostly mild in severity, with few leading to treatment discontinuation.

Conclusion

Orismilast demonstrated early itch reduction NRS≥4 and statistically significant efficacy versus placebo at Week 16 as measured by IGA0/1. The study was impacted by a high EASI placebo rate; however, in severe patients, the 20 and 40 mg doses separated from placebo for EASI75 and EASI90 measurements, consistent with the overall findings as measured by IGA 0/1, patient-reported efficacy, and objective biomarkers.

No new safety signals were identified, and the profile was aligned with the well-established experience from the PDE4 inhibitor class. The most frequent TEAEs were gastrointestinal-related and headache.

These data confirm the clinical relevance of high potency PDE4B/D selective inhibition with orismilast, potentially offering a convenient, novel, oral therapy for the treatment of AD and other inflammatory diseases.

Keywords: atopic dermatitis, PDE4B, PDE4D, treatment, oral administration

Conflicts of interest

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