Results from ADVISE: a randomized, double-blind, placebo-controlled phase 2 study of etrasimod, an oral, selective, sphingosine 1-phosphate receptor modulator, in adults with moderate-to-severe atopic dermatitis

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Goals: Etrasimod is an oral, once-daily, selective sphingosine 1-phosphate (S1P) receptor 1,4,5 ($S1P_{1,4,5}$) modulator in development for multiple immune-mediated inflammatory disorders. $S1P_1$ regulates migration of lymphocytes out of lymphatic tissues and dendritic cell migration to lymph nodes. Etrasimod acts as a functional antagonist by inducing sustained receptor internalization of the $S1P_1$ receptors, preventing lymphocyte migration from lymphatic tissue and reduction in peripheral lymphocytes available for recruitment to sites of inflammation without broad immunosuppression. In atopic dermatitis (AD), skin-resident dendritic cells engulf foreign antigens and allergens, then traffic to the lymph nodes where they activate naïve T cells. Activated T cells migrate from lymphatic tissues to skin and drive inflammation by secreting cytokines and chemokines and recruiting other immune cells such as eosinophils and mast cells. $S1P_1$ functional antagonism in modulating the trafficking of dendritic cells, T cells, and eosinophils support the potential for etrasimod as a novel therapeutic agent for reducing skin inflammation in AD. Results from pre-clinical models of AD supported the mechanism of action of etrasimod in reducing skin inflammation and dermatitis. Etrasimod was well tolerated and effective in a Phase 2 trial in moderate-to-severely active ulcerative colitis and is under investigation for other immune-mediated conditions, including alopecia areata, eosinophilic esophagitis, and Crohn's disease. This study assessed the efficacy and safety of etrasimod, the first oral S1P receptor modulator to be evaluated in patients with moderate-to-severe AD.

Methods: ADVISE (NCT04162769) is a multicenter, randomized, double-blind, placebo-controlled, 12-week phase 2 study. Key inclusion criteria were age 18-70 years, chronic AD ≥1 year prior to screening, baseline Eczema Area and Severity Index (EASI) score ≥16, validated Investigator's Global Assessment (vIGA) score ≥3, body surface area ≥10% of AD involvement, and recent history of inadequate response to topical medications or for whom topical treatment was inadvisable. After a 1-week run-in with emollient, participants were randomized 1:1:1 to once-daily etrasimod 1 mg or 2 mg or placebo. The primary efficacy endpoint was percent change in EASI from baseline at Week 12. A key secondary endpoint was achievement of vIGA score of 0 or 1 with a reduction from baseline of ≥2, the Food and Drug Administration recommended endpoint for a new drug approval for AD.

Results: 140 participants were randomized (etrasimod 1 mg, n=47; etrasimod 2 mg, n=47; placebo, n=46) and 80% completed the 12-week double-blind treatment period. Most participants (82.9%) had moderate vIGA-AD scores at baseline. The proportion of participants receiving etrasimod 2 mg who achieved vIGA 0 or 1 increased over time without plateau of effect. At Week 12, a significantly greater proportion of participants receiving etrasimod 2 mg vs placebo achieved vIGA 0 or 1 (29.8% vs 13.0%, *P*=0.0450). Percent improvement from baseline in EASI score was significantly greater with etrasimod 2 mg vs placebo at Week 4 (38.4% vs 23.4%, *P*=0.0232) and numerically superior at Week 12 (56.8% vs 48.5%; *P*=0.1966). A posthoc treatment completer analysis excluding participants with dose interruption showed significant improvements at Week 12 for etrasimod 2 mg vs placebo in proportion of participants achieving vIGA 0 or 1 (36.8% vs 13.0%; *P*=0.0115). Percent improvement from baseline in EASI score was significantly greater with etrasimod 2 mg vs placebo at Week 4 (39.8% vs 23.7%; *P*=0.0195) and Week 12 (62.1% vs 48.8%; *P*=0.0414) without plateau of effect. Etrasimod 1 mg did not demonstrate statistical difference from placebo in either vIGA 0 or 1 or in percent improvement in EASI at Week 12. There were no reported serious adverse events (SAEs). In participants receiving etrasimod, the most common AEs (>5% and greater than placebo) were nausea, constipation, back pain, and dizziness. One participant each in the etrasimod 2 mg and placebo group reported dyspnea as an AE. There were no reported cardiac AEs, venous thromboembolism, macular edema, or opportunistic or serious infections in participants receiving etrasimod.

Conclusions: Treatment with etrasimod showed dose-dependent efficacy with the 2 mg dose showing significant separation from placebo at both Weeks 4 and 12 across key efficacy endpoints and no plateau of effect at Week 12, as well as good tolerability. These results support the rationale of $S1P_{1,4,5}$ receptor modulation as a viable mechanism of action for the treatment of AD and warrants further investigation in phase 3 clinical trials.

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