Clinically meaningful improvements in patient-reported outcomes and itch: analysis of a phase 2 clinical trial in adults with moderate to severe atopic dermatitis treated with etrasimod, a novel, oral selective sphingosine 1-phosphate receptor modulator

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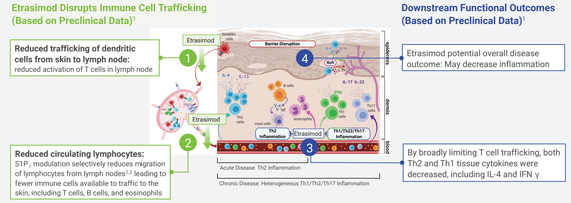
BACKGROUND

S1P RECEPTOR MODULATION WITH ETRASIMOD POTENTIALLY INTERRUPTS MULTIPLE PATHWAYS THAT MEDIATE ACUTE AND CHRONIC DISEASE PHASES OF ATOPIC DERMATITIS (AD)

Etrasimod is a selective sphingosine 1-phosphate 1, 4, and 5 receptor ($S1P_{1,4,5}$) modulator



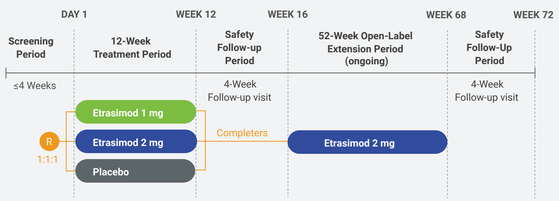
AD, atopic dermatitis; $S1P_1$, sphingosine 1-phosphate receptor 1.

EVALUATING THE EFFECT OF ETRASIMOD ON QUALITY OF LIFE IN AD

- Etrasimod is a once-daily, oral $S1P_{1,4,5}$ modulator being evaluated in multiple immune-mediated inflammatory diseases, including alopecia areata, ulcerative colitis, Crohn's disease and eosinophilic esophagitis
- The Phase 2 ADVISE study[4] of etrasimod (NCT04162769) was the first to evaluate S1P receptor modulation as a potential mechanism for treatment of patients with moderate-to-severe AD
- Intense itch is a primary cause of reduced health-related quality of life in patients with AD and is associated with sleep disturbances and resulting fatigue[5,6]
- The effect of etrasimod on itch and quality of life was evaluated in ADVISE as secondary and exploratory outcomes

STUDY DESIGN

Study enrolled 140 participants in sites across the US, Canada, and Australia



- Inclusion Criteria
  - Male and female participants 18–70 years of age
  - Eczema Area and Severity Index (EASI) ≥16 at baseline
  - Validated Investigator Global Assessment (vIGA) ≥3
  - Body Surface Area (BSA) involvement ≥10%
- Primary Endpoint
  - Percent change in EASI from baseline to Week 12
- Key Secondary Endpoint
  - Proportion of participants with a vIGA of 0 or 1 and reduction from baseline of ≥2 points at Week 12
- Patient-Reported Outcomes
  - Peak pruritus NRS (office-based; collected at the clinic visits only as single points)
  - Dermatology Life Quality Index (DLQI)
  - Patient-Oriented Eczema Measure (POEM)

RESULTS

- Most participants (89.2%) had moderate vIGA-AD scores

Table 1. Demographics and Baseline Characteristics (Full Analysis Set [N=140])

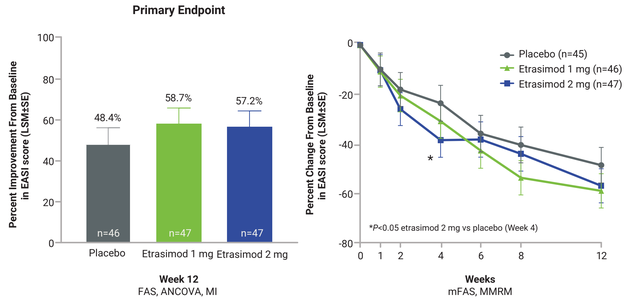
	Placebo (n=46)	Etrasimod 1 mg (n=47)	Etrasimod 2 mg (n=47)	All (N=140)
Age (years), mean (SD)	44.1 (16.2)	41.7 (13.3)	41.8 (14.8)	42.5 (14.7)
Sex, female, n (%)	27 (58.7)	30 (63.8)	29 (61.7)	86 (61.4)
Race, n (%)				
White	31 (67.4)	27 (57.4)	26 (55.3)	84 (60.0)
Asian	2 (4.3)	2 (4.3)	3 (6.4)	7 (5.0)
Black or African American	11 (23.9)	15 (31.9)	18 (38.3)	44 (31.4)
Other Combined*	2 (4.4)	3 (6.4)	0 (0)	5 (3.5)
EASI, mean (SD)	25.7 (10.6)	25.6 (8.5)	25.5 (10.6)	25.6 (9.9)
vIGA, n (%)				
3 = Moderate	39 (84.8)	38 (80.9)	39 (83.0)	116 (82.9)
4 = Severe	7 (15.2)	9 (19.1)	8 (17.0)	24 (17.1)
BSA AD Involvement (%), mean (SD)	30.9 (17.9)	38.8 (24.6)	33.2 (20.4)	34.3 (21.2)
Peak Pruritus NRS, mean (SD)	7.6 (2.0)	8.0 (2.2)	8.2 (1.8)	7.9 (2.0)

*Other Combined comprises American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and Other.
AD, atopic dermatitis; BSA, body surface area; EASI, Eczema Area and Severity Index; NRS, numerical rating scale; vIGA, validated Investigator Global Assessment.

EFFICACY

- Percent reduction in EASI from baseline to Week 12 was 57.2% in the etrasimod 2 mg group and 48.4% in the placebo group
- At Week 4, percent reduction in EASI from baseline was significantly greater with etrasimod 2 mg compared with placebo (P=0.0232)

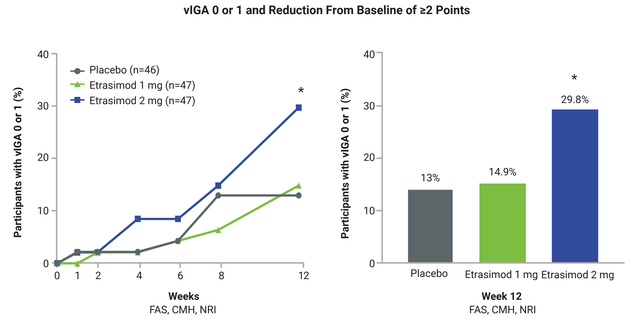
Figure 1. Percent Improvement in EASI From Baseline at Week 12 and Over Time



ANCOVA, analysis of covariance; EASI, Eczema Area and Severity Index; FAS, Full Analysis Set; LSM, least squares mean; mFAS, modified Full Analysis Set; MI, multiple imputation; MMRM, mixed model repeated measures; SE, standard error.

- 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)

Figure 2. Proportion of Participants Achieving vIGA Success Over Time and at Week 12

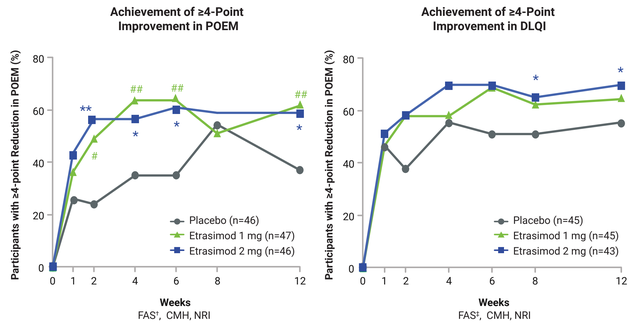


*P<0.05 vs placebo.

CMH, Cochran-Mantel-Haenszel; FAS, Full Analysis Set; NRI, non-responder imputation; vIGA, validated Investigator Global Assessment.

- A significantly greater proportion of participants receiving etrasimod 2 mg vs placebo achieved a ≥4-point improvement from baseline in POEM at Weeks 2, 4, 6, and 12
- A significantly greater proportion of participants receiving etrasimod 2 mg vs placebo achieved a ≥4-point improvement from baseline in DLQI at Weeks 8 and 12

Figure 3. Improvement in POEM and DLQI Over Time

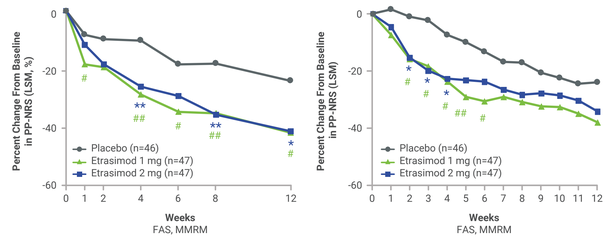


*P<0.05 etrasimod 2 mg vs placebo. †P<0.05 etrasimod 1 mg vs placebo.
**P<0.01 etrasimod 2 mg vs placebo. ††P<0.01 etrasimod 1 mg vs placebo.

CMH, Cochran-Mantel-Haenszel; DLQI, Dermatology Life Quality Index; FAS, Full Analysis Set; NRI, non-responder imputation; POEM, Patient-Oriented Eczema Measure.
†Among patients with baseline POEM ≥4.
‡Among patients with baseline DLQI ≥4.

- A significantly greater proportion of participants achieved a ≥4-point improvement from baseline in office-based PP-NRS receiving etrasimod 1 mg vs placebo at Weeks 2, 4, 6 and 8, and etrasimod 2 mg vs placebo at Weeks 8 and 12
- Significant improvements in diary-based PP-NRS were observed in participants receiving etrasimod 1 mg at Weeks 2, 3, 4, 5, and 6, and 2 mg at Weeks 2, 3, and 4

Figure 4. Improvement in Office-Based and Patient Diary-Based Peak Pruritus NRS



* P<0.05 etrasimod 2 mg vs placebo.
** P<0.01 etrasimod 2 mg vs placebo.
# P<0.05 etrasimod 1 mg vs placebo.
P<0.01 etrasimod 1 mg vs placebo.
FAS, Full Analysis Set; LSM, least squares mean; MMRM, mixed model repeated measures; NRS, numerical rating scale; PP-NRS, peak pruritus NRS. Office-based PP-NRS is the maximum score the participant gave when asked on the intensity of their itch over the previous 7 days. Office-based peak pruritus NRS was collected at the clinic visits only as single points vs weekly average of pruritus collected using patient daily diaries.

SAFETY

- There were no reported serious adverse events (SAEs)
- There were no reported cardiac AEs, venous thromboembolism, macular edema, or opportunistic or serious infections in participants receiving etrasimod; one participant each in the etrasimod 2 mg and placebo group reported dyspnea as an AE

Table 2. Overall Summary of Adverse Events in ≥5% of Participants in any Treatment Group

	Placebo (n=46)	Etrasimod 1 mg (n=47)	Etrasimod 2 mg (n=47)
Participants with any TEAE*	22 (47.8)	19 (40.4)	28 (59.6)
Treatment-emergent adverse events, n (%)			
Nausea	2 (4.3)	1 (2.1)	3 (6.4)
Constipation	0 (0)	0 (0)	3 (6.4)
Urinary tract infection	3 (6.5)	0 (0)	3 (6.4)
Back pain	1 (2.2)	0 (0)	3 (6.4)
Dizziness	1 (2.2)	2 (4.3)	3 (6.4)
Headache	4 (8.7)	1 (2.1)	0 (0)
Atopic dermatitis	4 (8.7)	0 (0)	2 (4.3)
≥1 serious adverse event, n (%)	0 (0)	0 (0)	0 (0)

*There were 8 Grade 1-3 TEAEs of lymphocyte decrease in the etrasimod groups: one in 1 mg and 7 in the 2 mg group which are not shown in the table. Lymphocyte count decrease is an on-target effect of etrasimod and the means by which the investigational drug potentially confers therapeutic benefit. Therefore, these lymphocyte-related AEs have not been included in the TEAE list.
AE, adverse event; TEAE, treatment-emergent AE.

CONCLUSIONS

- Etrasimod 2 mg resulted in significant improvements in the patient-reported outcomes POEM and DLQI compared with placebo
- Treatment with etrasimod 2 mg resulted in significant improvement in itch as measured by office-based peak pruritus NRS compared with placebo; results are consistent with peak pruritus NRS collected via patient diaries
- Etrasimod was well tolerated in patients with atopic dermatitis and the safety profile was consistent with previous trials. There were no serious adverse events in the study
- These data support the further assessment of the effect of etrasimod on itch and quality of life in atopic dermatitis in the next phase of clinical development

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