A Randomized, Double-Blind, Placebo-Controlled Trial of a Selective, Oral Sphingosine 1-Phosphate (S1P) Receptor Modulator, Etrasimod (APD334), in Moderate to Severe Ulcerative Colitis (UC): Results From the OASIS Study

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Introduction: The efficacy and safety of etrasimod, a selective, oral S1P receptor 1, 4, and 5 modulator, was evaluated in patients (pts) with moderate-severe UC.

Methods: This randomized, double-blind, parallel-group, 12-week (wk) phase 2 induction study evaluated etrasimod in pts with moderate-severe UC, defined as 3-component Mayo Clinic Score (MCS) of 4–9 with endoscopic subscore ≥2 and rectal bleeding (RB) subscore ≥1. The 3-component MCS (range 0–9) includes RB, stool frequency, and endoscopy. Pts received once-daily etrasimod 1 mg (n=52) or 2 mg (n=50), with no dose titration, or placebo (PBO; n=54). The primary endpoint (EP) was change from baseline (BL) in 3-component MCS at wk 12. Secondary EPs included the proportion of pts with endoscopic remission (≤1 point). Exploratory EPs included the proportion of pts achieving clinical remission and clinical response at wk 12 and change in lymphocyte count (LC). Changes in MCS were assessed by analysis of covariance with treatment as a factor and current oral corticosteroid (CS)use, prior anti-tumor necrosis factor (TNF)α use, and BL measures as covariates; LC was assessed by mixed-effects model and parameters with proportions of pts by the Mantel-Haenszel method with adjustment for current oral CS and prior anti-TNFα use.

Results: Of 156 pts randomized, 90% completed the study. BL characteristics, including age, sex, disease duration, current CS use, prior biologic use, were balanced among groups. At wk 12, dose-dependent

improvement occurred with etrasimod in all efficacy measures vs PBO (Table). Etrasimod 2 mg improved change from BL in 3-component MCS vs PBO (difference, 0.99 points; 90% CI, 0.30–1.68; *P*=0.009) (Figure). More pts receiving etrasimod 2 mg achieved endoscopic improvement (41.8% vs 17.8% for PBO; *P*=0.003). At wk 12, there was a significant decrease in circulating LCs from BL with etrasimod 1 and 2 mg relative to PBO (37.2% and 57.3%, respectively; *P*<0.001 for both). Adverse events (AEs) were mostly mild to moderate and similar among groups. More PBO-treated pts (11.1%) had a serious AE (SAE) vs etrasimod-treated pts (2 mg, 0%; 1 mg, 5.8%), reflecting disease worsening. No SAEs related to bradycardia or atrioventricular block were noted.

Discussion: In pts with moderate- severe UC, etrasimod was more effective than PBO in achieving dose-dependent improvements in clinical response, clinical remission, and endoscopic appearance. Etrasimod was safe and well tolerated in this short-term study.

Table. Efficacy Results at Week 12

Efficacy Measure	PBO (n=54)	Etrasimod 1 mg (n=52)	Etrasimod 2 mg (n=50)
Primary Endpoint:			
Change from baseline in 3-component MCS (RB + SF + endoscopy),	–1.50	–1.94	–2.49
LS mean difference vs PBO[a]		–0.43	–0.99
		P=0.146	*P*=0.009
Secondary Endpoint:			
Patients with endoscopic improvement (MCS 0 or 1), %	17.8	22.5	41.8
Difference vs PBO[b]		4.1	24.4
		P=0.306	*P*=0.003
Exploratory Endpoints:			
Patients with clinical response, %	32.5	43.7	50.6
Difference vs PBO[b]		11.4	18.9
		P=0.131	*P*=0.028
Patients with clinical remission, %	8.1	16.0	33.0
Difference vs PBO[b]		7.1	25.8
		P=0.136	*P*<0.001

LS, least-squares; MCS, Mayo Clinic Score; PBO, placebo; RB, rectal bleeding; SF, stool frequency
[a]Analysis model estimated difference from PBO for some measures using analysis of covariance with treatment as a factor and current oral corticosteroid use, prior anti-TNFα use, and baseline value as covariates.
[b]Difference of proportion using Mantel-Haenszel model and adjusted for current oral corticosteroid and prior anti-TNFα use.
P values are 1-sided vs PBO.

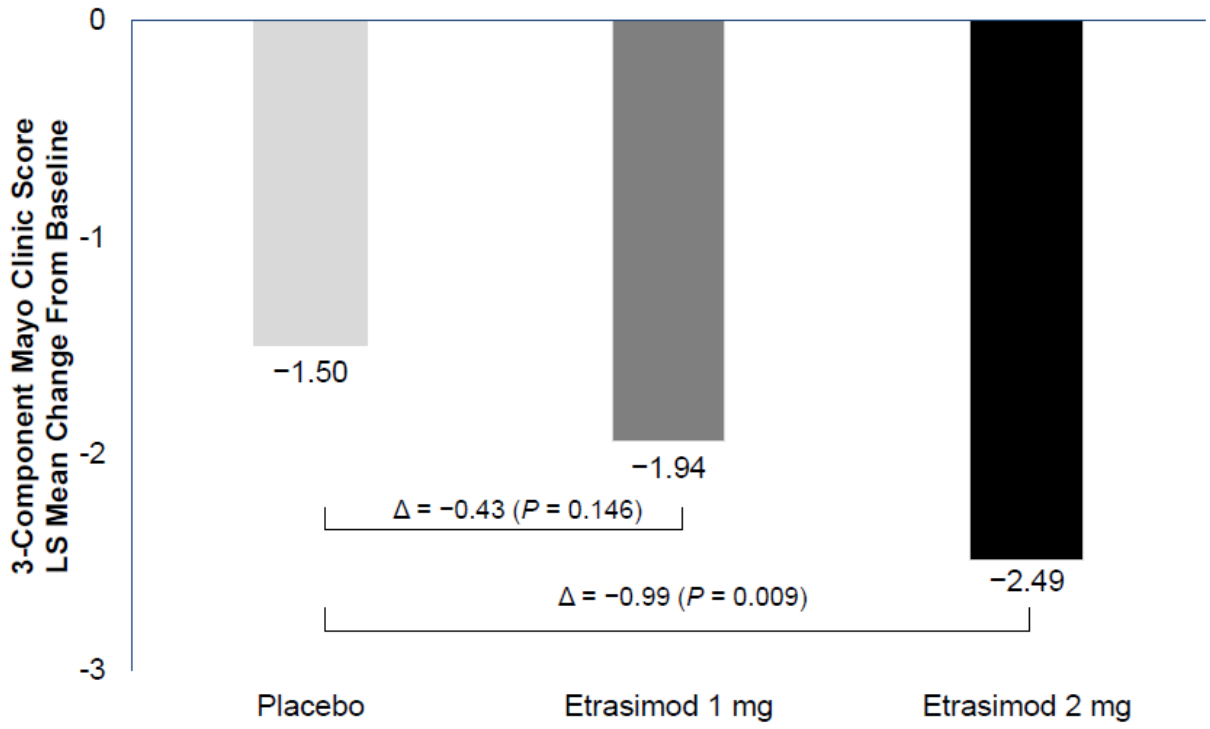

Figure. Primary Endpoint Results at Week 12.
LS, least-squares; Δ, LS mean difference from placebo. Difference from placebo was estimated using analysis of covariance with treatment as a factor and current oral corticosteroid, prior anti-TNFα use, and baseline value as covariates.