Histologic remission and mucosal healing in a randomized, placebo-controlled, phase 2 study of etrasimod in patients with moderately to severely active ulcerative colitis

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Background: Etrasimod (APD334), an oral, selective sphingosine-1-phosphate receptor modulator, was evaluated in the randomized, double-blind, placebo-controlled, parallel-group, phase 2 OASIS study (ClinicalTrials.gov identifier: NCT02447302) in patients with moderately to severely active ulcerative colitis (UC). Etrasimod demonstrated dose-dependent improvements in clinical response, clinical remission, and endoscopic appearance and decreased circulating lymphocytes. Here, we describe histologic remission and mucosal healing results at week 12.

Methods: Patients were randomized to receive once-daily etrasimod 1 mg (n=52) or 2 mg (n=50), with no dose titration, or placebo (n=54). At baseline and week 12, endoscopic severity was assessed by sigmoidoscopy with central readings using the Mayo endoscopic subscore. Biopsies were taken, and histology results were scored by a blinded central pathologist using the Geboes index. Prespecified endpoint definitions were endoscopic improvement (Mayo endoscopic subscore of 0 or 1); histologic improvement (Geboes score <3.1); and histologic remission (Geboes score <2.0). Mucosal healing (a post hoc analysis) was defined as both endoscopic improvement and histologic remission. Differences between groups were estimated using the Mantel–Haenszel analysis adjusted for current corticosteroid use at baseline and prior anti-tumor necrosis factor alpha use.

Results: Of 156 patients randomized, 90% completed the study. Etrasimod 2 mg, compared with placebo, resulted in significantly more patients who achieved endoscopic improvement (43.2% vs 16.3%, respectively; *P*=0.003), histologic improvement (31.7% vs 10.2%; *P*=0.006), and histologic remission (19.5% vs 6.1%; *P*=0.027) at week 12 (Table). Mucosal healing was seen in 19.5% and 4.1% of patients treated with etrasimod 2 mg and placebo, respectively (*P*=0.010). More patients receiving etrasimod 1 mg also achieved each endpoint compared with placebo; however, results did not reach statistical significance.

Conclusion: Etrasimod 2 mg induced significantly higher rates of endoscopic improvement, histologic improvement and remission, and mucosal healing in patients with moderately to severely active UC when compared with placebo. Mucosal healing may prove to be an achievable and objective measure of drug efficacy in UC induction studies.

Table. Endoscopic, Histologic, and Mucosal Measures at Week 12

Efficacy Measure	Etrasimod 1 mg (n=49)	Etrasimod 2 mg (n=41)	Placebo (n=49)
Endoscopic improvement (Mayo endoscopic subscore ≤1)			
Patients achieving, %	22.0[a]	43.2[b]	16.3
Difference from placebo[c] (90% CI)	5.1 (−7.7 to 18.0)	25.9 (11.0 to 40.8)	
	P=0.261	*P*=0.003	
Histologic improvement (Geboes score <3.1)			
Patients achieving, %	20.4	31.7	10.2
Difference from placebo[c] (90% CI)	9.9 (−1.8 to 21.7)	21.2 (7.5 to 35.0)	
	P=0.090	*P*=0.006	
Histologic remission (Geboes score <2.0)			
Patients achieving, %	10.2	19.5	6.1
Difference from placebo[c] (90% CI)	3.4 (−5.7 to 12.5)	13.3 (1.9 to 24.8)	
	P=0.271	*P*=0.027	
Mucosal healing[d] (Both endoscopic improvement and histologic remission)			
Patients achieving, %	8.2	19.5	4.1
Difference from placebo[c] (90% CI)	3.6 (−4.3 to 11.5)	15.4 (4.3 to 26.4)	
	P=0.231	*P*=0.010	

CI, confidence interval. Modified intention-to-treat population. All *P* values are 1-sided. [a]n=50; [b]n=44; [c]Mantel–Haenszel estimate, adjusted for current corticosteroid use at baseline and prior anti-tumor necrosis factor alpha use; [d]Post hoc analysis.