CHARACTERIZATION OF EARLY CLINICAL AND PHARMACOKINETIC RESPONSE PROFILES OF VEDOLIZUMAB: AN INTERIM ANALYSIS OF ENTERPRET, A PHASE 4 CLINICAL STUDY

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Introduction: Vedolizumab (VDZ), a gut-selective antibody that binds specifically to integrin α4β7, is approved for treatment of adults with moderate-to-severe ulcerative colitis (UC). An association between VDZ levels and clinical remission during induction therapy at Week (Wk) 6 was observed in pivotal trial data; the majority of nonresponders at Wk 6 had VDZ levels <40 μg/mL, and those with VDZ clearance >0.14 L/d had reduced efficacy outcomes (Osterman MT, et al. Aliment Pharmacol Ther. 2019). In the ongoing randomized controlled trial (ENTERPRET), we are evaluating whether dose escalation starting at Wk 6 in clinical nonresponders with high VDZ clearance (level <50 μg/mL) at Wk 5 leads to improved outcomes at Wk 30. This is an interim analysis of ENTERPRET in which baseline predictors of response at Wk 6 were investigated.

Methods: Adults with moderately to severely active UC received VDZ 300 mg IV on Day 1 and Wk 2. At Wk 5, VDZ concentration in serum was measured; clinical response was assessed at Wk 6 based on partial Mayo score (reduction in partial Mayo score ≥2 points and ≥25% from baseline [Day 1] with an accompanying decrease in rectal bleeding subscore ≥1 point or absolute rectal bleeding score ≤1 point). Descriptive analysis was used for these interim data, including baseline characteristics in responder and nonresponder groups.

Results: A total of 117 patients (mean age 41.2 years, 40.2% female) were analyzed; 112 were classified as a responder (n=55) or nonresponder (n=57). Baseline VDZ levels were higher in nonresponders vs responders (9.5 vs 7.1 years), with 47.4% of nonresponders having disease duration ≥7 years compared with 38.2% of responders. Endoscopic activity score was higher in nonresponders vs responders (49.1% vs 36.4% had severely active disease [Mayo endoscopic subscore=3]). 63.2% of nonresponders had a high stool frequency at baseline (Mayo score=3) compared with 49.1% of responders, 63.6% of responders had more severe rectal bleeding scores (Mayo subscore of 2–3) compared with 45.6% of nonresponders. More responders (67.3%) were anti-TNF–naive at baseline than nonresponders (52.6%). At Wk 6, change in mean (SD) partial Mayo score from baseline was −4.2 (1.65) for responders and −0.2 (0.96) for nonresponders. Wk 5 mean VDZ serum concentrations were numerically lower in responders (31.5 [SD=15.3] μg/mL) vs responders (40.3 [SD=12.8] μg/mL) in responders. There were no unexpected treatment-emergent adverse events in either group.

Conclusion: Interim data from ENTERPRET show Wk 6 responders had higher VDZ serum concentrations at Wk 5 than nonresponders. Although current results are consistent with the hypothesis that lower response to VDZ at Wk 6 correlates with lower drug exposure, we await the final results of ENTERPRET to better understand the exposure-response relationship of VDZ.