P065
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 ≥5% 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=57) or nonresponder (n=55). At Wk 6, 39.7% of responders (95% 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 subscore=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-naïve 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 nonresponders (31.2 [SD=12.8] vs 40.3 [SD=15.3] 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.

P066
GB004, A NOVEL GUT-TARGETED PROLYL HYDROXYLASE INHIBITOR FOR INFLAMMATORY BOWEL DISEASE: FIRST-IN-HUMAN, MULTIPLE-DOSE STUDY IN HEALTHY SUBJECTS WITH GUT BIOPSIES
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Background: GB004 is a small molecule polyl hydroxylase inhibitor (PHDI) that stabilizes hypoxia inducible factors (HIF1-α), key transcription factors involved in the protective cellular responses at the intersection of hypoxia and inflammation. GB004 was selected based on its gut-targeted profile to limit systemic on-target effects associated with HIF1α stabilization. Consistent with this, orally administered GB004 in a healthy non-human primate model engaged HIF-related genes in the gut, and, in animal models of colitis, demonstrated a significant reduction in disease activity, improvements in histologic measures, and greater exposure in GI tissue relative to plasma. GB004 is in clinical development for treatment of inflammatory bowel disease (IBD) and was shown to be safe in a single ascending dose study. The study described here evaluates the safety, tolerability, and pharmacokinetics (PK) of multiple daily doses of GB004 in plasma and colon biopsies.
Methods: This was a randomized, double-blind, placebo-controlled, multiple dose, Phase 1a study conducted in healthy subjects at a single site in Canada. Three dose levels of GB004 formulated as a solution or placebo solution were administered orally once a day for 8 days; safety and PK were evaluated. Plasma levels of HIF-target genes EPO and VEGF were determined by immunoassays from samples collected at pre-dose, 4, 8, and 12 hours post dose on Day 1 and Day 7. Colon biopsies were obtained one day prior to first dose and at Day 8.
Results: 42 subjects (20 male and 22 female) were dosed. No serious adverse events or deaths were recorded. The most commonly observed gastrointestinal adverse event in GB004-treated subjects was dizziness (31%;10/32); all events were mild and did not result in study drug discontinuation. There were no identified risks of GB004. Following oral dosing, GB004 was rapidly absorbed and eliminated from the systemic