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CHARACTERIZATION OF EARLY CLINICAL AND PHARMACOKINETIC RESPONSE PROFILES OF VELODIZUMAB: AN INTERIM ANALYSIS OF ENTERPRET, A PHASE 4 CLINICAL STUDY
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Introduction: Velo dizumab (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) based on Wk 6 response. At baseline, mean disease duration was higher in nonresponders than 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%) with 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 ≥3) compared with 45.6% of nonresponders. More responders (67.3%) were anti-TNF-α-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 nonresponders (31.5 [SD=12.8] μg/mL) than responders (50.3 [SD=15.3] μg/mL in response; 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.

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GB004, A NOVEL GUT-TARGETED PROLYL HYDROXYLASE INHIBITOR FOR INFLAMMATORY BOWEL DISEASE: FIRST-IN-HUMAN, MULTIPLE-DOSE STUDY IN HEALTHY SUBJECTS WITH GUT BIOPSY
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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 inhibit systemic on-target effects associated with HIF1-α 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 pharmacokinetic (PK) effects associated with GB004 in adults with moderate-to-severe inflammatory bowel disease (IBD) and UC.

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 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 unexpected treatment-related 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.

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Conclusions: This study demonstrated that multiple daily doses of GB004 solution were safe and tolerated. The PK profile was consistent with its intended preferential exposure in the gut. In support of the gut-targeted exposure, HIF target genes EPO and VEGF were not modulated in plasma. A clinical study of GB004 is ongoing in patients with ulcerative colitis to explore safety, PK, and pharmacodynamics both systemically and within colonic tissue (NCT03860896). A tablet formulation is also being developed.

IMPACT OF MIRIKIZUMAB TREATMENT ON HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH ULCERATIVE COLITIS: A PHASE 2 STUDY ANALYSIS USING THE SF-36 V2 STANDARD

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Background: Mirikizumab (LY3074828) is a humanized monoclonal antibody directed against the p19 subunit of IL-23, and has demonstrated efficacy in ulcerative colitis (UC), and Crohn’s disease. The effect of miri on health-related quality of life (HRQoL) as measured by the 36-Item Short Form Health Survey v2 Standard (SF-36) was examined in a Phase 2, multicenter, randomized, parallel-arm, double-blind placebo (PBO)-controlled trial (NCT02891226) in patients with moderate to severe active UC.

Methods: Patients were randomized 1:1:1:1 to receive intravenous PBO, miri 50mg or 200mg with possibility of exposure-based (EB) dose increases, or fixed miri 600mg every 4 weeks (Q4W), with efficacy assessment at Week 12. Patients with clinical response to miri at Week 12 were re-randomized 1:1 to a double-blind maintenance treatment of miri 200mg subcutaneously (SC) Q4W or 12 weeks (Q12W) and were treated through Week 52. The SF-36, a 36-item patient-completed questionnaire with recall period past 4-weeks, that measures 8 domains (physical functioning, role-physical, role-emotional, bodily pain, vitality, social functioning, mental health, and general health) and two summary scores, physical component summary (PCS) and mental component summary (MCS), was assessed at baseline and at Weeks 4, 8, 12, 24, 32, and 52. Treatment comparisons were evaluated using mixed effects for repeated measures for mean improvement of PCS, MCS, and domain score changes with treatment, geographic region, and prior biologic UC therapy use as factors.

Results: The PCS was significantly higher in all miri doses at Week 12 (Least Squares Mean [LSM] ± SE; PBO: 45.4±0.8; miri 50mg: 48.2±0.9, p=0.011; 200mg: 48.0±0.8, p=0.022; 600mg: 49.0±0.9, p=0.002; Fig 1A), while the MCS was significantly higher in the miri 200mg and 600mg groups (PBO: 42.5±1.2; miri 50mg: 43.8±1.3; 200mg: 46.1±1.2, p=0.002; 600mg: 48.1±1.3, p<0.001; Fig 1B). Of the 8 SF-36 domains, 7 (physical functioning, role-physical, role-emotional, social functioning, vitality, bodily pain, and mental health) showed statistically significant improvement at Week 12 in at least one miri dose group compared to PBO, while 1 (general health) demonstrated a numerical improvement (Fig 1C). Patients who continued onto randomized maintenance treatment sustained the improved scores through Week 52 (Fig 2). These results paralleled the observed treatment associated benefits on clinical response and remission rates at Weeks 12 and 52.

Conclusion: Mirikizumab treatment results in significant improvements in patient HRQoL demonstrated by significantly improved SF-36 scores after 12 weeks of induction treatment, which were sustained during an additional 40 weeks of maintenance treatment.

MIRIKIZUMAB TREATMENT IMPROVES BOWEL MOVEMENT URGENCY IN PATIENTS WITH MODERATELY TO SEVERELY ACTIVE ULCERATIVE COLITIS

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Background: Mirikizumab (miri; LY3074828) is a humanized monoclonal antibody directed against the p19 subunit of IL-23, which demonstrated efficacy and was well-tolerated in a phase 2 randomized clinical trial (NCT02589665) in patients with ulcerative colitis (UC). Bowel movement urgency is one of the most bothersome symptoms experienced by patients with UC with an often-overlooked impact of their quality of life (QoL). Here we show the effect of miri on patient-reported urgency.

Methods: Patients were randomized 1:1:1:1 to receive intravenous placebo (PBO), miri 50mg or 200mg with possibility of exposure-based dose increases, or fixed miri 600mg every 4 weeks (Q4W), with efficacy assessment at Week 12. Patients who achieved clinical response to miri at Week 12 (decrease in 9-point Mayo score ≥ 2 points and ≥ 35% from baseline, and either a decrease in rectal bleeding [RB] sub-score ≥ 1 or RB sub-score of 0 or 1) were re-randomized 1:1 to double-blind maintenance treatment with miri 200mg subcutaneously (SC) every 4 (Q4W) or 12 (Q12W) weeks and were treated through Week 52. Patients reported daily symptoms, including absence or presence of bowel movement urgency. Logistic regression analysis was conducted to evaluate the treatment differences in absence of urgency among patients who had urgency at baseline for the first 12 weeks, with absence of urgency defined as no urgency symptom for three consecutive days prior to each scheduled visit. The proportion of patients with no urgency was calculated for the maintenance period among patients who had urgency at baseline and reached clinical response at Week 12, irrespective of urgency status at Week 12. Patients who had missing urgency data were imputed as having experienced urgency.

Results: At Week 12 patients in the 200mg and 600mg miri groups showed significantly higher rates of achieving absence of urgency compared to the PBO group (PBO: 10/55, 18.2%; [CI: 8.0–28.4]; miri 50mg: 18/59, 30.5%; [CI: 18.8–42.3]; 200mg: 22/58, 39.3%; [CI: 26.5, 52.1], p=0.016; 600mg: 22/51, 43.1%; [CI: 29.5, 56.7], p=0.006, Figure 1). Induction clinical responders who continued onto the maintenance period sustained this improvement in urgency with minimal variation (Figure 2).

Conclusion: In patients who reported bowel movement urgency at baseline, mirikizumab treatment resulted in significantly higher proportions of patients with no bowel movement urgency compared to placebo at Week 12, with numerical improvement observed as early as Week 4 and statistically significant improvement by Week 8. The reduction in bowel movement urgency was sustained through Week 52.