

Efficacy and safety of icanbelimod (CBP-307) in adults with moderate-to-severe ulcerative colitis: A phase 2, randomized, double-blind, placebo-controlled trial

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Background: We evaluated icanbelimod, a selective small-molecule sphingosine-1-phosphate-1 (S1P₁) receptor modulator, as induction and maintenance therapy for moderately-to-severely active ulcerative colitis (UC).

Methods: CN002 was a Phase 2, dose-ranging trial (NCT04700449) in which patients with active UC (adapted Mayo score >4 with endoscopic sub-score ≥2) were randomized (1:1:1) to oral QD icanbelimod 0.1 mg (n=39), 0.2 mg (n=53) or placebo (n=53) for 12-weeks of induction treatment and 36-weeks of maintenance. The primary outcome was mean change in adapted Mayo score from baseline to Week 12. Secondary outcomes were mean change in complete Mayo score, clinical remission (rectal bleeding (RB)=0; stool frequency ≤1; endoscopy sub-score ≤1), clinical response (Mayo decrease of ≥2 points and ≥30%, and a decrease of ≥1 in RB or an absolute RB ≤1) and mucosal healing (endoscopic sub-score ≤1). Patients with clinical response at the end of induction continued their assigned treatment [0.1 mg (n=12), 0.2 mg (n=21) or placebo (n=13)]; non-responders (n=40) received open-label icanbelimod 0.2 mg for up to 36 weeks.

Results: The icanbelimod 0.1 mg arm was terminated during the induction period due to lack of effect in a concurrent Crohn's disease trial. Accordingly, all results reported herein are for the icanbelimod 0.2 mg group comparison with placebo. Baseline characteristics were similar between the icanbelimod and placebo groups. A >50% mean reduction (by $0.8 \times 10^9/L$) in lymphocyte count was observed in the active treatment group. For the primary endpoint, icanbelimod demonstrated a non-significant overall change in adapted Mayo score ($\Delta=-0.64$, $P=0.094$). However, nominal statistical significance for icanbelimod relative to placebo was observed for multiple secondary endpoints based upon complete Mayo scores at Week 12, including mean change in complete Mayo score ($\Delta=-0.93$, $P=0.04$), clinical remission ($\Delta=15.0\%$, $P=0.026$), and clinical response ($\Delta=22.1\%$, $P=0.022$). Clinical remission and clinical response differences based upon adapted Mayo score definitions also favored icanbelimod ($\Delta=18.7\%$, $P=0.016$ and $\Delta=20.1\%$, $P=0.039$, respectively). Mucosal healing rates were not significantly different ($\Delta=9.0\%$, $P=0.295$). Icanbelimod and placebo group patients

with Grade ≥ 3 treatment-emergent adverse events (TEAEs; 7.5% vs 7.7%) and serious TEAEs (3.8% vs 5.8%), respectively. Sinus bradycardia events (all Grade 1 severity) were reported at higher incidences in icanbelimod (9 [17.0%]) compared to placebo (3 [5.8%]) and typically limited to initial dosing or up-titration during first week of treatment.

A total of 21 Icanbelimod responders entered maintenance with 81% (17/21) completing 48-weeks and 65% (11/17) achieving clinical remission. Additionally, 80% (8/10) achieving clinical remission at end of induction, sustained it through Week 48. Overall, 57% (12/21) with clinical response at end of induction achieved clinical remission at end of maintenance. Maintenance safety remained consistent with findings observed during induction.

Conclusions: In this dose-ranging Phase 2 trial, icanbelimod significantly improved key outcomes, including complete Mayo score, clinical response and clinical remission (a key FDA regulatory endpoint) at Week 12 and sustained clinical remission, through Week 48 in patients who achieved clinical remission following 12 weeks of induction therapy. Icanbelimod was well tolerated. Further investigation of optimal doses is warranted to better enhance therapeutic response.

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