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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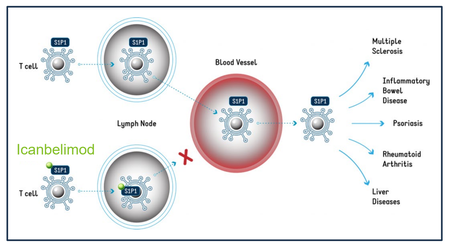
Poster #2



- Icanbelimod (formerly CBP-307) is a potent next-generation S1P1 modulator, with no notable activity for S1P3.
- In two Phase 1 trials with healthy adults in China and Australia, mean absolute lymphocyte count (ALC) decreased by as much as 79.3% and recovered quickly (one week) after treatment discontinuation.[1,2]
- In this Phase 2 trial, we evaluated icanbelimod as induction and maintenance therapy for moderate-to-severe UC.

Methodology

Study design

CN002 was a Phase 2 dose-ranging trial (NCT04700449). Sixty-four study centers in China, Pakistan, Ukraine, and the USA participated. The first participant was enrolled in December 2018 and the last participant completed in November 2022.

Adults with moderate-to-severe UC (adapted Mayo score ≥4, endoscopic subscore ≥2) were randomized 1:1:1, double-blind, to icanbelimod 0.1 mg, 0.2 mg or placebo QD for 12-weeks induction therapy, orally administered within 30 minutes of breakfast. Clinical responders at Week 12 (based on adapted Mayo score; defined below) entered a 36-week double-blind maintenance phase, while non-responders received open-label icanbelimod 0.2 mg QD, followed by 4-weeks safety follow-up.

During the induction and open-label phases, patients underwent dose titration (0.05 mg on Days 1–4, 0.1 mg on Days 5–7, and target dose from Day 8).

Endpoints and statistics

The primary endpoint for icanbelimod 0.2 mg, and a secondary endpoint for icanbelimod 0.1 mg, was change in adapted Mayo score (range 0–9; 0–3 subscores for stool frequency, rectal bleeding, and endoscopy) at Week 12. Change in complete Mayo score (adapted Mayo, plus 0–3 for physician's global assessment of severity) at Week 12 was a secondary endpoint.

Binary endpoints were:

Clinical response, based on adapted and complete Mayo score

- adapted Mayo score reductions of ≥2 points and ≥30%, and ≥1-point decrease in rectal bleeding or absolute rectal bleeding ≤1 point.
- complete Mayo score reductions of ≥3 points and ≥30%, decrease of ≥1 point in rectal bleeding or absolute rectal bleeding ≤1 point.

Clinical remission, based on adapted and complete Mayo score

- adapted Mayo score rectal bleeding 0, stool frequency ≤1, endoscopic ≤1 (excluding friability).
- complete Mayo score ≤2, with no individual subscore >1.

Mucosal healing: Mayo endoscopic subscore ≤1.

Statistical analysis of change in Mayo score comprised of multiple imputation for missing scores at Week 12 and an ANCOVA model with baseline as covariate. For binary endpoints, patients with missing data were considered as non-responders in analyses using the Cochran Mantel Haenszel test. Both tests were stratified by whether prior treatment with TNFα antagonists had failed.

Results

Patient characteristics and disposition

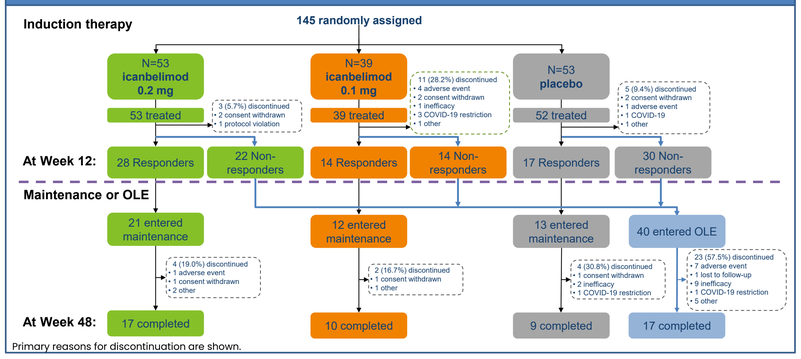
At baseline, disease characteristics (Table 1) and demographics were generally well balanced per treatment group. In the overall population, mean (SD) age was 42.0 (11.1) years, BMI 22.5 (3.7) kg/m², and most patients were Asian (91.7%) and male (62.8%).

Recruitment into the icanbelimod 0.1 mg QD group was terminated early because of lack of effect in a simultaneous Crohn's disease trial. No patients discontinued icanbelimod 0.2 mg induction therapy primarily due to inefficacy (Figure 1).

Table 1: Baseline disease characteristics

Mean (SD), unless stated otherwise	Icanbelimod 0.2 mg QD N=53	Icanbelimod 0.1 mg QD N=39	Placebo QD N=53
TNFα treatment failed, n (%)	2 (3.8)	1 (2.6)	2 (3.8)
Adapt Mayo score	5.91 (1.30)	5.95 (1.48)	5.97 (1.20)
Complete Mayo score	8.10 (1.45)	8.11 (1.64)	8.16 (1.31)
Time since UC diagnosis, years	5.63 (5.69)	5.03 (4.34)	5.93 (6.06)
Colonoscopy in the last 12 months, n (%)	34 (64.2)	33 (84.6)	39 (73.6)
Location and extent of UC			
Proctosigmoiditis	11 (20.8)	4 (10.3)	9 (17.0)
Left sided colitis	7 (13.2)	9 (23.1)	8 (15.1)
Extensive colitis	7 (13.2)	11 (28.2)	7 (13.2)
Pancolitis	6 (11.3)	5 (12.8)	8 (15.1)
Other	3 (5.7)	4 (10.3)	7 (13.2)

Figure 1: CN002 patient disposition



Primary reasons for discontinuation are shown.

Improvements in clinical remission, response, and lymphocyte counts at Week 12

Icanbelimod 0.2 mg versus placebo QD resulted in a non-significant trend towards a reduction in adapted Mayo score (Δ = −0.64; p = 0.094), and a significant reduction in complete Mayo score (Δ = −0.93; p = 0.044), at Week 12 of induction therapy (Figure 2).

Improvements in clinical remission and clinical response (Figure 3) were compatible with ALC (51.3% reduction at Week 12) (Figure 4).

Figure 2: Change in Mayo score at Week 12

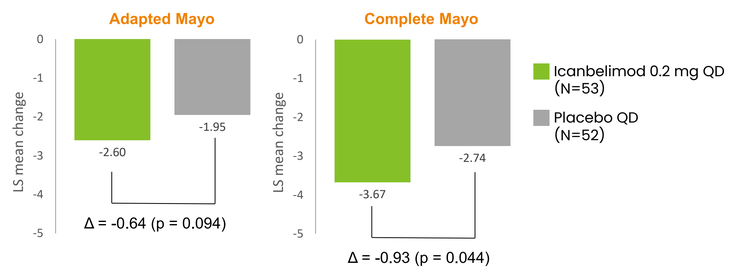


Figure 3: Clinical remission, response, and mucosal healing at Week 12

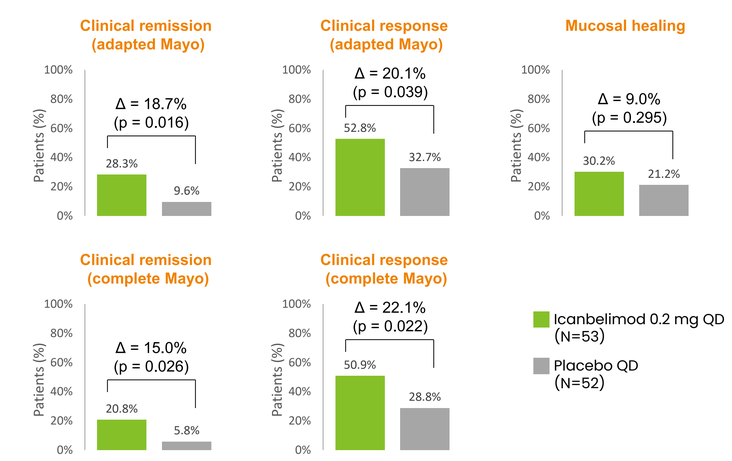
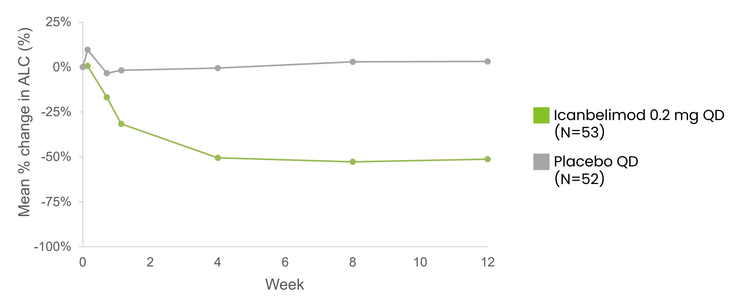


Figure 4: Absolute lymphocyte count (ALC) at Week 12



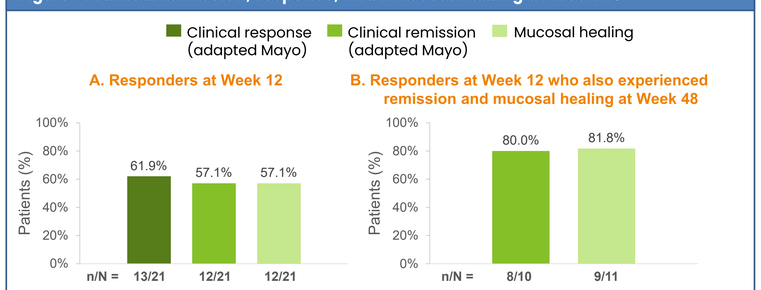
Efficacy sustained at Week 48

Of 28 patients who achieved clinical response (based on adapted Mayo) at Week 12 in the icanbelimod 0.2 mg QD group, 21 patients entered the 36-week maintenance phase (Figure 1).

Of the 21 patients, clinical response (based on adapted Mayo) was sustained at Week 48 with icanbelimod 0.2 mg QD maintenance therapy by 61.9% of patients, while 57.1% experienced clinical remission (based on adapted Mayo) and 57.1% experienced mucosal healing (Figure 5A).

In *post hoc* analyses, with the subsets of the 21 clinical responders who experienced clinical remission based on adapted Mayo (n=10) and mucosal healing (n=11) at Week 12, these efficacy responses were sustained by 80.0% (n=8/10) and 81.8% (n=9/11) of patients at Week 48, respectively (Figure 5B).

Figure 5: Clinical remission, response, and mucosal healing at Week 48



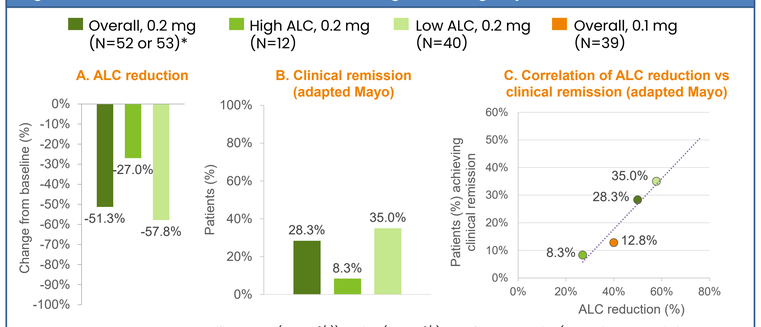
All patients in the analyses were treated with icanbelimod 0.2 mg QD induction and maintenance therapy.

Potentially greater efficacy at higher doses than tested in the current study

The 51.3% reduction in ALC at Week 12 (Figure 6) was less than the 79.3% achieved with the same dose (0.2 mg QD) in a Phase 1 trial with healthy adults,[1] suggesting greater room for improvement at even higher doses than the highest (0.2 mg QD) tested in the current study. Ozanimod and etrasimod also achieve less ALC reduction at a given dose in UC patients than in healthy individuals.[3,4]

In a *post hoc* subgroup analysis, patients with greater reductions in ALC at Week 12 (57.8%, n=40) than obtained *a priori* for the overall population in the icanbelimod 0.2 mg QD arm (51.3%, n=53) (Figure 6A) tended to experience greater efficacy, including a higher clinical remission rate (35.0% vs 28.3%) (Figure 6B). When these data were included in a correlation analysis, a positive relationship was observed between ALC reduction and clinical remission rate (Figure 6C).

Figure 6: ALC vs remission, based on low and high ALC subgroups, at Week 12



Lymphocyte counts at Week 12 were classified as 'low' (≤1.0 x 10^9/L)) or 'high' (>1.0 x 10^9/L). N=52 for ALC reduction (one patient had a missing post-baseline ALC value), N=53 for clinical remission.

Safety outcomes

Most patients reported TEAEs in each treatment group (Tables 2 and 3), mainly Grade 1 in severity. No cardiac TEAEs were classified as serious or led to study drug withdrawal. Most TEAEs were related to UC and previous medical history; the most common serious TEAE was colitis ulcerative.

All TEAEs of special interest, TEAEs leading to study drug withdrawal, and serious TEAEs resolved or were resolving, with one exception, i.e. respiratory disorder, a TEAE of special interest, which was Grade 1, not classified as serious, and did not lead to withdrawal from the icanbelimod 0.2 mg induction therapy group. Other TEAEs of special interest in the icanbelimod 0.2 mg group at Week 12 were sinus bradycardia and macular thickening (each n=1). In the icanbelimod 0.1 mg group, TEAEs of special interest at Week 12 were hepatic function abnormal (n=3), liver injury, sinus bradycardia, and macular edema (each n=1). The sinus bradycardia events of special interest occurred during dose titration. At Week 12, across the three treatment groups, TEAEs of hepatic function abnormal (n=8), liver injury (n=1), and sinus bradycardia (n=16) occurred that were not classified as TEAEs of special interest because they did not meet prespecified criteria.

Table 2: TEAEs across 12 weeks of induction therapy

n (%)	Icanbelimod 0.2 mg QD N=53	Icanbelimod 0.1 mg QD N=39	Placebo QD N=52
Any TEAE (none were fatal)[a]	47 (88.7)	37 (94.9)	40 (76.9)
Serious TEAE[b]	2 (3.8)	6 (15.4)	3 (5.8)
Drug-Related Serious[b]	1 (1.9)	2 (5.1)	0
TEAE Leading to Study Drug Withdrawal	2 (3.8)	6 (15.4)	0
TEAE of Special Interest	3 (5.7)	6 (15.4)	0

[a]One patient experienced a Grade 4 drug-related TEAE (hypernatremia), which resolved spontaneously, in the 0.1 mg group. Grade 3 drug-related TEAEs were colitis ulcerative (n=2), hepatic function abnormal and liver injury in the 0.1 mg group (each n=1); aspartate aminotransferase increased, white blood cell count decreased, anemia in the 0.2 mg group (each n=1).

[b]The most common serious TEAE was colitis ulcerative in the icanbelimod 0.2 mg (n=4), 0.1 mg (n=2) and placebo groups (n=2). The other serious TEAEs (none drug related) reported by Week 12 across the treatment arms were gastritis, transitional cell carcinoma, and ovarian cyst (each n=1).

Table 3: TEAEs across 36 weeks of maintenance or open-label extension therapy

n (%)	Icanbelimod 0.2 mg QD N=53	Icanbelimod 0.1 mg QD N=39	Placebo QD N=52	Open-label 0.2 mg QD N=40
Any TEAE (none were fatal)[a]	20 (95.2)	11 (91.7)	12 (92.3)	33 (82.5)
Serious TEAE[b]	1 (4.8)	0	0	8 (20.0)
Drug-Related Serious	0	0	0	2 (5.0)
TEAE Leading to Study Drug Withdrawal	1 (4.8)	0	0	5 (12.5)
TEAE of Special Interest	3 (14.3)[c]	0	1 (7.7)	5 (12.5)

[a]Drug-related Grade 3 TEAEs were lymphocyte decrease in the 0.2 mg group, hypertension in the 0.1 mg group, and neutrophil count decreased, hepatic function abnormal, cytomegalovirus infection, and colitis ulcerative in the open-label group (each n=1).

[b]Serious TEAE were appendicitis in the 0.2 mg group (n=1) and colitis ulcerative (n=6), chronic gastritis, large intestine polyp, anal abscess, cholera, and cytomegalovirus infection in the open-label group (each n=1).

[c]Only one of these TEAE of special interest represented a new event reported; the other two events were initially reported in the induction therapy phase.

Conclusions

- In this dose-ranging Phase 2 trial, orally administered icanbelimod was well tolerated and significantly improved key outcomes, including complete Mayo score, clinical response and clinical remission (a key FDA regulatory endpoint) at Week 12.
- Most clinical responders at Week 12 demonstrated continued efficacy with 36 weeks of maintenance therapy.
- Our findings suggest that patients with UC would likely derive greater clinical benefit with higher doses than icanbelimod 0.2 mg QD, the maximum administered in this Phase 2 dose-ranging trial, which will thus be investigated in the Phase 3 trial program.

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References: 1. Chen et al. Manuscript in preparation. 2. Lickliter et al. Manuscript in preparation. 3. Tran et al. J Clin Pharmacol. 2017; 57:988-96. 4. Sandborn et al. Gastroenterology. 2020; 158:550-61.

Abbreviations: ALC, absolute lymphocyte count; ANCOVA, analysis of covariance; BMI, body mass index; LS, least squares; OLE, open-label extension; QD, once daily; SD, standard deviation; S1P1, sphingosine-1-phosphate receptor subtype 1; TEAE, treatment-emergent adverse event; UC, ulcerative colitis.