Study design
CNO202 was a Phase 2 dose-ranging trial (NCT04700443). Sixty-four study centers in China, Pakistan, Ukraine, and the USA participated. The first patient was enrolled in December 2018 and the last participant completed in November 2022.

Adults with moderate-to-severe UC (adapted Mayo score ≥4, endoscopic sub-score ≥2) were randomized 1:1:1:1 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, where non-responders received open-label icanbelimod 0.2 mg QD, followed by 4-weeks safety follow-up.

Endpoints and statistics
The primary endpoint was change in adapted Mayo score at Week 12 (adapted Mayo score, complete Mayo score, score ≤2 with no notable activity for S1P3). Clinical responders were defined as complete Mayo score ≤2 (ranging from 0–12), including the “adenoma” subscore (range 0–3) in patients with no endoscopic active inflammation.

Results

Patient characteristics and disposition
At baseline, disease characteristics (Table 1) and demographics were generally well balanced between treatment groups. In the overall population, mean (SD) age was 42.0 (11.1) years, BMI 22.5 (3.7) kg/m², and 50% of patients were female. 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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Icanbelimod 0.2 mg N=41</th>
<th>Icanbelimod 0.1 mg N=39</th>
<th>Placebo QD N=52</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) age</td>
<td>42.0 (11.1)</td>
<td>41.7 (11.8)</td>
<td>41.9 (11.8)</td>
</tr>
<tr>
<td>Mean BMI</td>
<td>22.5 (3.7)</td>
<td>22.5 (3.7)</td>
<td>22.5 (3.7)</td>
</tr>
<tr>
<td>Gender (%)</td>
<td>Male: 58%</td>
<td>Male: 51%</td>
<td>Male: 50%</td>
</tr>
<tr>
<td></td>
<td>Female: 42%</td>
<td>Female: 49%</td>
<td>Female: 50%</td>
</tr>
</tbody>
</table>

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 69.0% of patients, while 57.5% experienced mucosal healing (based on adapted Mayo) and 57.5% experienced mucosal healing (Figure 5A).

In post hoc analyses, with the subset of the 21 patients who experienced clinical remission (adapted Mayo score ≤2) and mucosal healing (N=21) at Week 12, these efficacy responses were sustained by 80.0% (N=17) and 86.5% (N=16) of patients at Week 48, respectively (Figure 5B).

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 (key FDA regulatory endpoints) 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 who did not achieve clinical response and remission at Week 12 were likely to continue to achieve these endpoints during extended treatment with icanbelimod 0.2 mg QD. This is the first large Phase 2 trial to report results from a randomized, double-blind, placebo-controlled trial of icanbelimod 0.2 mg QD in adults with moderate-to-severe UC.