Remibrutinib treatment improves hive severity in patients with chronic spontaneous urticaria: Phase 2b study results

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Introduction and Objective

- Chronic spontaneous urticaria (CSU) is characterized by the occurrence of wheals (hives) and/or angioedema for ≥6 weeks and has a major impact on patients’ well-being\(^1\)

- Second-generation H1-antihistamine are recommended as first-line treatment for CSU\(^1\)

- Remibrutinib is a novel, oral, highly selective BTK inhibitor that offers fast disease control in CSU patients who remain symptomatic despite H1-antihistamine.\(^2,3\) Remibrutinib is currently in Phase 3 development for the treatment of CSU (REMIx-1: NCT05030311\(^4\), REMIX-2: NCT05032157\(^5\))

- Remibrutinib showed robust clinical efficacy, with a fast onset and a favorable safety profile for up to 12 weeks in the Phase 2b study (NCT03926611) which was sustained up to 52 weeks in the open-label Phase 2b extension study (NCT04109313) in patients with moderate to severe CSU who remain symptomatic with H1-antihistamine\(^3,6\)

**Objective**

To explore the effect of remibrutinib on hive severity in patients with CSU from the Phase 2b study

BTK, bruton’s tyrosine kinase; CSU, chronic spontaneous urticaria.
Study design

A dose-finding, multicenter, randomized, double-blind, placebo-controlled Phase 2b study in patients with CSU (NCT03926611)

*Eligible patients rolled over into an extension study (NCT04109313) at Week 12 or at Week 16, following roll-over criteria defined in the extension study protocol and dependent on HA/EC approval from participating countries. Background therapy was a 2nd generation H1-antihistamine at a locally approved licensed posology that had to be administered daily with a stable treatment regimen throughout the study. Rescue therapy was a 2nd generation H1-antihistamine at a locally approved licensed posology that differed from the background H1-antihistamine, was eliminated primarily via renal excretion, and could only be given to treat unbearable symptoms (itch) of CSU on a day-to-day basis.

b.i.d., twice daily; CSU, chronic spontaneous urticaria; EC, ethical committee; HA, health authority; n, number of patients randomized in each group; q.d, once daily.


*
Methods

Study assessments

- Change from baseline in UAS7 and HSS7 at Weeks 2, 4, and 12
- Proportion of patients with HSS7=0 (no hives) at Weeks 2, 4, and 12

*The hives (wheals) severity score, defined by number of hives, was recorded by the subject twice daily in their eDiary on a scale of 0 (none) to 3 (>12 hives/12 hours)*

Data analysis

- The UAS7 was the sum of the HSS7 score and the ISS7 score. The possible range of the weekly UAS7 score was 0 – 42
- A weekly score (HSS7) was derived by adding up the average daily scores of the 7 days preceding the visit. The possible range of the weekly score was therefore 0 – 21

ISS7, weekly Itch Severity Score; HSS7, weekly Hives Severity Score; UAS7, weekly Urticaria Activity Score.
Patient demographics and baseline disease characteristics were generally balanced between treatment arms (randomized set)

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Phase 2b Core Study</th>
<th>Remibrutinib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>42.5±16.04</td>
<td>44.0±16.47</td>
<td>45.2±13.40</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>35 (79.5)</td>
<td>30 (68.2)</td>
<td>39 (83.0)</td>
</tr>
<tr>
<td>Baseline UAS7 score</td>
<td>31.4±7.06</td>
<td>31.2±7.22</td>
<td>28.5±7.00</td>
</tr>
<tr>
<td>Duration of CSU (years)</td>
<td>6.2±7.71</td>
<td>5.9±8.82</td>
<td>5.3±5.82</td>
</tr>
<tr>
<td>Baseline HSS7 score*</td>
<td>16.9±4.35</td>
<td>17.6±3.92</td>
<td>15.9±4.22</td>
</tr>
<tr>
<td>Previous exposure to anti-IgE therapy, n (%)</td>
<td>13 (29.5)</td>
<td>13 (29.5)</td>
<td>13 (27.7)</td>
</tr>
</tbody>
</table>

- The mean baseline HSS7 was similar between any remibrutinib dose (15.6–17.6) and placebo (15.9)

*based on Full analysis set.
Data are presented as mean±SD, unless stated otherwise.
b.i.d., twice a day; CSU, chronic spontaneous urticaria; HSS7, weekly Hive Severity Score; N, total number of patients; q.d., once a day; SD, standard deviation; UAS7, weekly Urticaria Activity Score.
Remibrutinib (all doses) showed fast and significant improvement in UAS7 score over 12 weeks versus placebo

- UAS7 scores improved from baseline up to Week 12 in all remibrutinib doses compared with placebo
- A fast improvement in UAS7 was observed as early as at Week 1, which was maintained up to Week 12

Full analysis set.

b.i.d., twice daily; CI, confidence interval; LS, least square; N, number of patients; q.d., once daily; SE, standard error; UAS7, weekly Urticaria Activity Score.

Remibrutinib (all doses) showed higher reduction from baseline in HSS7 versus placebo over 12 weeks

- The mean reduction in HSS7 from baseline was higher with remibrutinib (any dose) versus placebo at Week 2 (reduction: 9.3 to 12.7 vs 2.1), Week 4 (reduction: 8.7 to 11.9 vs 2.6), Week 8 (reduction: 9.6 to 12.0 vs 3.6), and Week 12 (reduction 8.7 to 12.3 vs 4.5)

<table>
<thead>
<tr>
<th>Treatment arm</th>
<th>Week 2</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remibrutinib 10 mg q.d.</td>
<td>−11.7±7.32</td>
<td>−11.4±7.31</td>
</tr>
<tr>
<td>Remibrutinib 35 mg q.d.</td>
<td>−12.7±6.67</td>
<td>−12.3±7.12</td>
</tr>
<tr>
<td>Remibrutinib 100 mg q.d.</td>
<td>−9.3±6.54</td>
<td>−8.7±7.05</td>
</tr>
<tr>
<td>Remibrutinib 10 mg b.i.d.</td>
<td>−9.5±7.58</td>
<td>−10.3±7.96</td>
</tr>
<tr>
<td>Remibrutinib 25 mg b.i.d.</td>
<td>−11.2±7.03</td>
<td>−11.3±8.16</td>
</tr>
<tr>
<td>Remibrutinib 100 mg b.i.d.</td>
<td>−10.1±6.88</td>
<td>−11.4±6.64</td>
</tr>
<tr>
<td>Placebo (N=42)</td>
<td>−2.1±5.97</td>
<td>−4.5±7.41</td>
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</tbody>
</table>

Full analysis set.

b.i.d., twice a day; HSS7, weekly Hive Severity Score; N, number of patients; q.d., once a day; SD, standard deviation.
Proportion of patients achieving HSS7=0 was higher with remibrutinib (all doses) than with placebo*

A higher proportion of patients achieved HSS7=0 with remibrutinib versus placebo at Week 2 (21.3% to 34.9% vs 0%), Week 4 (21.3% to 48.8% vs 0%), and Week 12 (31.1% to 46.5% vs 14.3%)

*Non-responder imputation; Full analysis set.
b.i.d., twice a day; HSS7, weekly Hive Severity Score; n, number of patients who responded; N, number of patients; q.d., once a day; SD, standard deviation.
Key takeaways

- The present analysis from the Phase 2b dose-finding trial in patients with CSU inadequately controlled by $H_1$-antihistamines showed:
  
  - **Fast improvement** in UAS7 and HSS7 with remibrutinib (all doses) **as early as Week 2**, which was **sustained for up to Week 12** versus placebo
  
  - All doses of remibrutinib were more effective in attaining complete response on HSS7 versus placebo
  
- Phase 3 studies (REMIX-1: NCT05030311, REMIX-2: NCT05032157) are ongoing to confirm the findings of the Phase 2b study

CSU, chronic spontaneous urticaria; HSS7 weekly Hives Severity Score; UAS7, weekly Urticaria Activity Score.
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