Long-term treatment with remibrutinib shows favorable safety profile and sustained efficacy in patients with chronic spontaneous urticaria: Final results from the 52-week phase 2b extension study

Warner Carr¹, Jeffrey Tillinghast², Vipul Jain³, Sibylle Haemmerle⁴, Karine Lheritier⁴, Pauline Walsh⁵, Michael Wells⁶, Artem Zharkov⁴, Sophie Hugot⁴, Ana Giménez-Arnau⁷

¹Allergy and Asthma Associates of Southern California, and Southern California Research, Mission Viejo, California, USA; ²The Clinical Research Center, St. Louis, Missouri, USA; ³Division of Clinical Immunology and Allergy, Department of Medicine, McMaster University, Hamilton, Ontario, Canada; ⁴Novartis Pharma AG, Basel, Switzerland; ⁵Novartis Ireland Limited, Dublin, Ireland; ⁶Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA; ⁷Department of Dermatology, Hospital del Mar - IMIM, Universitat Pompeu Fabra, Barcelona Spain
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Introduction and study objective

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

- **Remibrutinib (LOU064)** is a novel, highly selective, potent, covalent **oral BTK inhibitor**\(^2\)

- In the preceding Phase 2b dose-finding core study (NCT03926611), remibrutinib showed **clinical efficacy and a favorable safety profile** for up to 12 weeks in patients with **moderate to severe CSU** inadequately controlled by \(H_1\)-antihistamines\(^3\)

- Here, we report 52-week data from the Phase 2b extension study

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**Objective**

To evaluate the long-term safety, tolerability, and efficacy of remibrutinib in patients with CSU in the open-label extension study

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BTK, Bruton’s tyrosine kinase; CSU, chronic spontaneous urticaria; CU, chronic urticaria.

Study design

52-week long-term open-label extension study of patients who completed preceding core study1-3

**Baseline**

- **Preceding study (core)** (NCT03926611) – 12 week treatment period and 4 week follow-up period; patients randomized to remibrutinib 10 mg, 35 mg, 100 mg (q.d., each), 10 mg, 25 mg, 100 mg (b.i.d., each), placebo (1:1:1:1:1:1:1).
- **UAS7<16 at Week 16 of core study.**
- **UAS7<16 at Week 12 or Week 16 of core study.**

**Visits (Weeks)**

- 0–12 weeks
- 12 weeks: Remibrutinib 100 mg b.i.d. (N=194)
- **Observational period** (Until UAS7≥16)
- **Follow-up** (Until UAS7≥16 at Week 12 or Week 16 of core study)

**Open-label treatment period (NCT04109313)**

- **Background therapy:** second-generation H1 antihistamine
- **Rescue therapy:** Alternative second generation H1 antihistamine

**Patients** who never relapsed (UAS7≥16 at least once) within 12 weeks completed the study at the end of the observational period.

**The minimum duration of the follow-up period was 4 weeks for all subjects who stopped treatment with remibrutinib. Patients who achieved a UAS7≥16 at Week 52 of the treatment period extended their follow-up period until they relapsed (UAS7≥16). Follow-up ended at Week 68 for all patients.**

**Background therapy** was a second generation H1-antihistamine at a locally approved licensed posology given with a stable treatment regimen. Administration of background H1-antihistamine after Week 4 was at the discretion of the investigator. Background therapy was not permitted from Day 1 until Week 4 of the treatment period.

**Rescue therapy** was a second generation H1-antihistamine at a locally approved licensed posology that was eliminated primarily via renal excretion. The rescue H1-antihistamine used differed from the background H1-antihistamine and was only given to treat unbearable symptoms (itch) of CSU on a day-to-day basis.

**b.i.d.,** twice a day; **N,** total number of patients; **q.d.,** once daily; **UAS7,** weekly Urticaria Activity Score

Methods

Study eligibility

• Completed core study according to protocol

Study endpoints

• Primary endpoint included occurrence of TEAEs (serious/non-serious)
• Other endpoints of interest included change from baseline in UAS7 and proportion of patients with a complete response to treatment (UAS7=0) at Week 52

Statistical analysis

• TEAEs were summarized as grouped (by primary system organ class) and as individual (by preferred term) events
• Change from baseline and UAS7 and proportion of patients achieving UAS7=0 at Week 52 were analyzed using summary statistics

TEAE, treatment-emergent adverse event; UAS7, weekly Urticaria Activity Score
Patient disposition

~80% patients completed the full 52-week treatment period*

*Study was conducted mostly during the COVID-19 pandemic phase; FPFV: 24 Oct 2019; LPLV: 09 Sep 2022

# All reasons with COVID-19 term are included in COVID-19 situation category

FPFV, first patient first visit; LPLV, last patient last visit; UAS7, weekly Urticaria Activity Score

Observational period (N=68)

UAS7<16 at Week 16 of core study

Patients who completed observational period without relapse or discontinued earlier: n=34

Number of patients entered open-label treatment period upon relapse (UAS7≥16): n=34

Open-label treatment period (N=194)

UAS7≥16 at Week 12 or Week 16 of core study

Completed n=156

Discontinued n=38

Primary reason for discontinuation:
- Subject decision: n=12
- Adverse event: n=11
- Lack of efficacy: n=11
- COVID-19 situation#: n=2
- Physician decision: n=1
- Pregnancy: n=1

Eligible patients who entered extension study from core study (N=230)
Demographics and baseline characteristics in the extension study were comparable to that of core study

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Extension study</th>
<th>Core study¹</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Remibrutinib 100 mg b.i.d. (N=194)</td>
<td>Total Randomized (N=311)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>45.5±14.1</td>
<td>45.0±14.9</td>
</tr>
<tr>
<td>Gender (female), n (%)</td>
<td>139 (71.6)</td>
<td>222 (71.4)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>77.8±17.9</td>
<td>78.1±18.0</td>
</tr>
<tr>
<td>Duration of CSU (years)</td>
<td>5.8±6.7</td>
<td>4.9±6.2</td>
</tr>
<tr>
<td>UAS7 score</td>
<td>27.9±8.2</td>
<td>29.6±7.1</td>
</tr>
<tr>
<td>Previous exposure to anti-IgE therapy, n (%)</td>
<td>54 (27.8)</td>
<td>84 (27.0)</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD unless stated otherwise

b.i.d., twice daily; CSU, chronic spontaneous urticaria; mg, milligram; IgE, immunoglobulin E; kg, kilogram; n, number of patients randomized to each arm; N, total number of patients; q.d., once daily; SD, standard deviation; UAS7, weekly Urticaria Activity Score

Safety and tolerability of 52-week remibrutinib 100 mg b.i.d treatment was comparable to any remibrutinib dose in the core study

<table>
<thead>
<tr>
<th>Overall safety profile</th>
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<td>Patients, n (%)</td>
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<tr>
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<th>Core study</th>
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<tr>
<td></td>
<td>Remibrutinib 100 mg b.i.d. (N=194)</td>
<td>Remibrutinib any dose (n=267)</td>
</tr>
<tr>
<td><strong>Duration of exposure, median (Q1–Q3) [weeks]</strong></td>
<td>52.1 (51.6–52.4)</td>
<td>12.1 (12.0–12.3)</td>
</tr>
<tr>
<td><strong>Patients with ≥1 TEAE</strong></td>
<td>139 (71.6)</td>
<td>155 (58.1)</td>
</tr>
<tr>
<td><strong>Discontinued study treatment due to TEAE(s)</strong></td>
<td>11 (5.7)</td>
<td>7 (2.6)</td>
</tr>
<tr>
<td><strong>Patients with SAE(s)</strong></td>
<td>6 (3.1)</td>
<td>5 (1.9)</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

- Overall, 71.6% patients experienced ≥1 TEAE with remibrutinib 100 mg b.i.d in extension study, with mostly mild (35.1%)* or moderate (32.5%)* in nature
- The proportion of patients with at least one event, events leading to treatment discontinuation and patients with serious events on remibrutinib treatment in the extension study was comparable to the core study
- No deaths occurred during core* or extension study
- The analysis of laboratory parameters, vital signs, and ECG findings did not reveal any significant safety concerns in the extension study similar to the core study
  - No trends of elevation of liver function tests from baseline were observed. Two notable newly occurring liver enzyme increases were both isolated ALT >3x and <5xULN with normal bilirubin levels, both returned to normal levels during the study

Here we report treatment-emergent AEs and SAEs only. MedDRA version 24.0 was used for reporting. *absolute numbers
ALT, alanine aminotransferase; b.i.d., twice a day; CTCAE, common terminology criteria for adverse events; ECG, electrocardiogram; MedDRA, Medical Dictionary for Regulatory Activities; N, total number of patients; n, number of patients in each arm; Q1–Q3, interquartile range; SAE, serious adverse event; TEAE, treatment-emergent adverse event; ULN, upper limit normal

Incidence of most frequent grouped and single events remained stable with long-term treatment with remibrutinib

<table>
<thead>
<tr>
<th>Safety events</th>
<th>Extension study</th>
<th>Core study</th>
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<tbody>
<tr>
<td></td>
<td>Remibrutinib 100 mg b.i.d. (N=194)</td>
<td>Remibrutinib any dose (n=267)</td>
</tr>
<tr>
<td>Events grouped by primary SOC in ≥10% patients in the 100 mg b.i.d. group in the extension study or any remibrutinib dose or placebo group in core study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>60 (30.9)</td>
<td>64 (24.0) 1</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>52 (26.8)</td>
<td>45 (16.9) 1</td>
</tr>
<tr>
<td>Gastrointestinal diseases</td>
<td>32 (16.5)</td>
<td>30 (11.2)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>26 (13.4)</td>
<td>24 (9.0)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>23 (11.9)</td>
<td>35 (13.1)</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>21 (10.8)</td>
<td>7 (2.6)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>20 (10.3)</td>
<td>10 (3.7)</td>
</tr>
</tbody>
</table>

Individual events by preferred term in ≥5% of patients in the 100 mg b.i.d. group in the extension study or any remibrutinib dose or placebo group in core study

<table>
<thead>
<tr>
<th>Event</th>
<th>Extension study</th>
<th>Core study</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSU</td>
<td>22 (11.3)</td>
<td>16 (6.0) 1</td>
</tr>
<tr>
<td>COVID-19</td>
<td>16 (8.2)</td>
<td>3 (1.1)</td>
</tr>
<tr>
<td>Headache</td>
<td>13 (6.7)</td>
<td>26 (9.7) 1</td>
</tr>
<tr>
<td>Eczema</td>
<td>10 (5.2)</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>8 (4.1)</td>
<td>23 (8.6) 1</td>
</tr>
</tbody>
</table>

• The higher rate of grouped skin and subcutaneous tissue disorder events was driven by events of CSU (11.3% in patients in extension study, of which 76% of events occurred on or after the last treatment day and 6.0% vs 2.4% in patients in core study)

• The higher incidence of COVID-19 events in extension study reflects the impact of COVID-19 pandemic

MedDRA version 24.0 was used for reporting. SOC, system organ class
b.i.d., twice a day; CSU, chronic spontaneous urticaria; COVID-19, coronavirus disease; MedDRA, Medical Dictionary for Regulatory Activities; N, total number of patients; n, number of patients
Events of special interest for BTK class remained stable with long-term treatment with remibrutinib beyond infections

<table>
<thead>
<tr>
<th>Incidence of events of special interest for BTK class, n (%)</th>
<th>Extension study</th>
<th>Core study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remibrutinib 100 mg b.i.d. (N=194)</td>
<td>Remibrutinib any dose (n=267)</td>
<td>Placebo (n=42)</td>
</tr>
<tr>
<td>Bleeding (platelet dysfunction)</td>
<td>12 (6.2)</td>
<td>18 (6.7)</td>
</tr>
<tr>
<td>Cytopenias (including neutropenia and lymphopenia)</td>
<td>2 (1.0)</td>
<td>8 (3.0)</td>
</tr>
</tbody>
</table>

- All reported bleeding events were minor in nature and all cytopenias were mild in severity
- Cytopenias continued to be rare with long-term treatment and not correlated with infectious events

MedDRA version 24.0 was used for reporting.
BTK, Bruton's tyrosine kinase; MedDRA, Medical Dictionary for Regulatory Activities; N, total number of patients; n, number of patients in each arm
Remibrutinib 100 mg b.i.d showed rapid and sustained improvement in UAS7, and more than half of the patients achieved UAS7=0 at Week 52

- At Week 52, the mean change from baseline in UAS7 with remibrutinib 100 mg b.i.d. was −21.8
- The percentage of patient achieving UAS7=0 increased during the study, with 55.8% of patients achieving UAS7=0 at Week 52

SD, standard deviation; UAS7, weekly Urticaria Activity Score
Conclusions

- The final analysis from Phase 2b extension study showed a favorable safety/tolerability profile with long-term exposure of remibrutinib 100 mg b.i.d. for up to 52 weeks in patients with CSU
  - The long-term safety profile of remibrutinib was consistent with the core study\(^1\) and interim analysis of Phase 2b extension data\(^2\)
- Remibrutinib showed fast and sustained efficacy for up to 52 weeks in patients with CSU inadequately controlled by H\(_1\)-antihistamines
- Remibrutinib is being assessed in ongoing Phase 3 clinical trials in CSU (REMIX-1 NCT05030311 and REMIX-2 NCT05032157)

**Remibrutinib is a potential new oral treatment option for patients with CSU**

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b.i.d., twice daily; CSU, chronic spontaneous urticaria