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Pooled REMIX-1/-2 Phase 3 Data: Early and Sustained Symptom Improvement With Remibrutinib in Chronic Spontaneous Urticaria

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KEY FINDINGS & CONCLUSIONS

- In the pooled REMIX-1/-2 studies, improvements in symptoms with remibrutinib were observed as early as week 1 and sustained to week 52
- Across REMIX-1 and REMIX-2, remibrutinib showed favorable safety and tolerability up to 52 weeks of treatment
- Remibrutinib has the potential to become a novel oral treatment option that provides fast and sustained symptom relief for patients with CSU inadequately controlled by H_1-AHs

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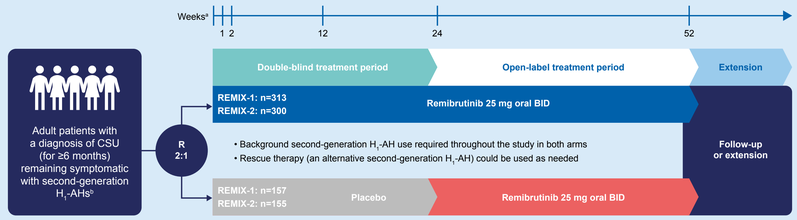
INTRODUCTION

- CSU is characterized by the spontaneous and recurrent appearance of itchy wheals, angioedema, or both, lasting >6 weeks[1,2]
- The recommended first-line treatment for CSU is second-generation H_1-AHs, including increased dosages of up to 4-fold the approved dose[1,3]; however, the majority of patients' disease remains uncontrolled with H_1-AHs[4–6]
- Remibrutinib is a novel, oral, highly selective Bruton's tyrosine kinase inhibitor that prevents mast cell-mediated release of histamine and other proinflammatory mediators[7,8]
- In a phase 2b study, remibrutinib showed a favorable safety profile and superior efficacy vs placebo in patients with CSU inadequately controlled by second-generation H_1-AHs[9]
- Here, we present pooled results from the phase 3 REMIX-1 (NCT05030311) and REMIX-2 (NCT05032157) studies, evaluating the efficacy and safety of remibrutinib in patients with CSU

METHODS

- REMIX-1 and REMIX-2 are multicenter, randomized, double-blind, placebo-controlled phase 3 studies investigating the safety and efficacy of remibrutinib
- Patients were randomized 2:1 to remibrutinib 25 mg BID or placebo (24 weeks), then all patients continued on open-label remibrutinib 25 mg BID (28 weeks) (**Figure 1**)
- In this analysis, data were analyzed using summary statistics based on the pooled population
- Pooled REMIX-1 and REMIX-2 mean (± SD) CFB in UAS7, ISS7, and HSS7 were assessed at weeks 1, 2, 12, 24, and 52 (a higher score reflects higher disease activity)
- Due to 2:1 randomization and the overall shorter exposure to placebo vs remibrutinib, safety outcomes were exposure-adjusted, calculated as the number of patients with an event per 100 patient-years (reported as EAIR)

Figure 1. Study Design for REMIX-1 and REMIX-2 Studies



[a]UAS7, ISS7, and HSS7 were collected throughout the study, in this analysis, UAS7, ISS7, and HSS7 scores are presented at weeks 1, 2, 12, 24, and 52.
[b]Presence of itch and hives for ≥6 consecutive weeks prior to screening despite the use of a second-generation H_1-AHs; UAS7 score ≥16, ISS7 score ≥6, and HSS7 score ≥6 during the 7 days prior to randomization (day 1).
BID, twice daily; CSU, chronic spontaneous urticaria; H_1-AH, H_1-antihistamine; HSS7, weekly hives severity score; ISS7, weekly itch severity score; R, randomized; UAS7, weekly urticaria activity score.

RESULTS

Demographics and Clinical Characteristics

- The pooled analysis included 606 and 306 patients in the remibrutinib and placebo groups who received at least one dose, respectively, from REMIX-1 and REMIX-2
- Patient demographics and baseline characteristics were well balanced between remibrutinib and placebo groups in both studies (**Table 1**)

Change From Baseline in UAS7, ISS7, and HSS7

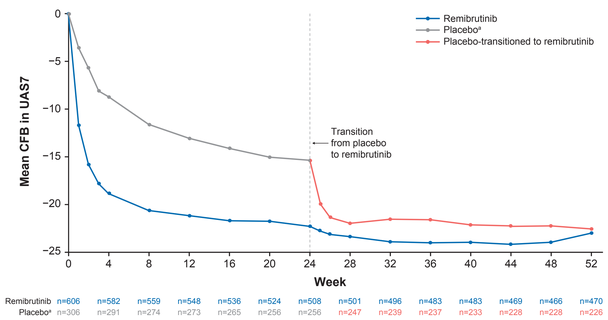
- Remibrutinib showed improvements vs placebo in mean (± SD) CFB-UAS7 as early as week 1 (**Figure 2**)
  - Week 1: –11.8 (± 9.9) vs –3.6 (± 7.6)
  - Week 2: –15.9 (± 12.3) vs –5.7 (± 9.2)
  - Week 12: –21.3 (± 11.9) vs –13.1 (± 12.1)
  - Week 24: –22.4 (± 11.9) vs –15.4 (± 13.3)
- Improvements were also shown in mean (± SD) CFB-ISS7 and CFB-HSS7 from week 1 to week 24 (**Figure 2**)
  - CFB-ISS7:
    - Week 1: –5.3 (± 4.7) vs –1.8 (± 3.6)
    - Week 2: –7.2 (± 5.9) vs –2.9 (± 4.6)
    - Week 12: –9.9 (± 5.8) vs –6.4 (± 5.9)
    - Week 24: –10.5 (± 5.8) vs –7.4 (± 6.4)
  - CFB-HSS7
    - Week 1: –6.4 (± 5.7) vs –1.8 (± 4.3)
    - Week 2: –8.7 (± 6.9) vs –2.8 (± 5.0)
    - Week 12: –11.3 (± 6.8) vs –6.7 (± 6.9)
    - Week 24: –11.9 (± 6.8) vs –8.0 (± 7.5)
- Improvements were sustained during the open-label treatment period. Patients receiving remibrutinib from initiation, and patients who transitioned to remibrutinib from placebo at week 24, showed similar improvements at week 52 (**Figure 2**)
  - UAS7: –23.1 (± 12.1) and –22.7 (± 11.9)
  - ISS7: –10.9 (± 5.9) and –10.7 (± 6.0)
  - HSS7: –12.2 (± 6.9) and –12.0 (± 6.7)

Safety

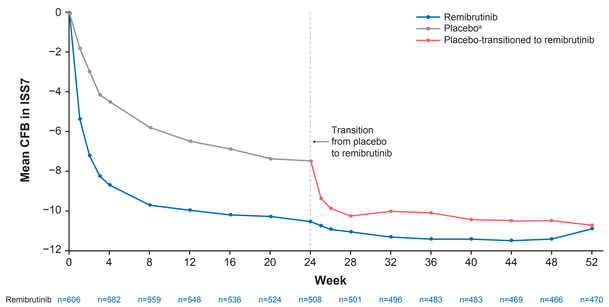
- Remibrutinib showed favorable safety and tolerability across the REMIX-1/-2 studies (**Table 2**)
- No deaths were reported, and discontinuation of study treatment due to AEs was infrequent
- No SAEs were considered related to the study medication by the investigator
- During the double-blind study period, the frequency of AEs was comparable between the remibrutinib (64.9% of patients) and placebo (64.7% of patients) groups
- The EAIR of AEs, SAEs, and AEs leading to treatment discontinuation, over the whole 52 week treatment period, was consistent with that seen in the double-blind treatment period
- The most frequent treatment-emergent AEs were COVID-19, nasopharyngitis, and headache (**Table 3**)

Figure 2. Improvement Over Time in UAS7, ISS7, HSS7 Change From Baseline (Full Analysis Set, Observed Data)

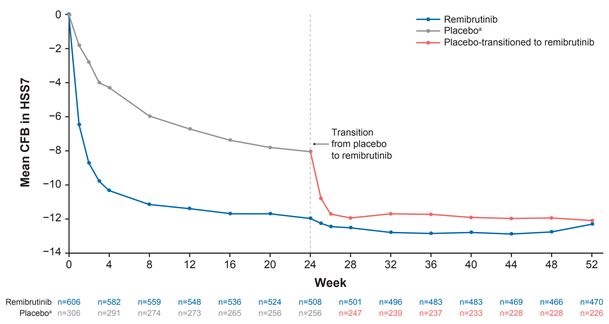
a) UAS7



b) ISS7



c) HSS7



[a]Patients in the placebo group transitioned to remibrutinib at week 24.

BID, twice daily; CFB, change from baseline; HSS7, weekly hives severity score; ISS7, weekly itch severity score; UAS7, weekly urticaria activity score.

Table 1. Pooled Baseline Disease Characteristics of REMIX-1 and REMIX-2

	Remibrutinib 25 mg BID (n=606)	Placebo[a] (n=306)	Total (N=912)
Baseline characteristics			
Age (years), mean ± SD	43.3 ± 14.4	43.7 ± 14.1	43.4 ± 14.3
Female, n (%)	403 (66.5)	204 (66.7)	607 (66.6)
BMI (kg/m^2), mean ± SD	27.4 ± 6.5	27.7 ± 6.3[b]	27.5 ± 6.4[c]
Duration of CSU (years), mean ± SD	6.2 ± 8.6	5.3 ± 6.7	5.9 ± 8.0
Baseline disease severity			
UAS7, mean ± SD	30.6 ± 7.8	29.7 ± 7.6	30.3 ± 7.7
ISS7, mean ± SD	14.6 ± 4.2	14.1 ± 4.0	14.4 ± 4.2
HSS7, mean ± SD	16.0 ± 4.5	15.6 ± 4.5	15.8 ± 4.5

[a]Patients in the placebo group transitioned to remibrutinib at week 24; [b]n=305; [c]n=911.
BID, twice daily; BMI, body mass index; CSU, chronic spontaneous urticaria; HSS7, weekly hives severity score; ISS7, weekly itch severity score; SD, standard deviation; UAS7, weekly urticaria activity score.

Table 2. Overview of Treatment-Emergent AEs During Entire Study Period of REMIX-1 and REMIX-2 (Safety Set)

	Double-blind study period (up to week 24)		Entire study period remibrutinib 25 mg BID (up to week 52) (n=606)	Placebo-transitioned to remibrutinib (weeks 24–52) (n=262)
n (%) EAIR [95% CI]	Remibrutinib 25 mg BID (n=606)	Placebo (n=306)		
Median duration of exposure, weeks	24.0	24.0	52.1	28.1
Participants with AE(s)	393 (64.9) 276.4 [249.7–305.1]	198 (64.7) 273.5 [236.8–314.4]	446 (73.6) 199.8 [181.7–219.3]	133 (50.8) 144.8 [121.2–171.6]
SAE(s)	20 (3.3) 7.7 [4.7–11.9]	7 (2.3) 5.3 [2.2–11.0]	25 (4.1) 4.7 [3.0–6.9]	3 (1.1) 2.1 [0.4–6.2]
Treatment discontinuation due to AE(s)	17 (2.8) 6.5 [3.8–10.3]	9 (2.9) 6.8 [3.1–13.0]	28 (4.6) 5.1 [3.4–7.4]	4 (1.5) 2.8 [0.8–7.2]

AE, adverse event; BID, twice daily; CI, confidence interval; EAIR, exposure-adjusted incidence rate; SAE, serious adverse event.

Table 3. Most Frequent (>3% in Any Treatment Group) Treatment-Emergent AEs, by Preferred Term During the Entire REMIX-1 and REMIX-2 Studies (Safety Set)

	Double-blind study period (up to week 24)		Entire study period remibrutinib 25 mg BID (up to week 52) (n=606)	Placebo-transitioned to remibrutinib (weeks 24–52) (n=262)
n (%) EAIR [95% CI]	Remibrutinib 25 mg BID (n=606)	Placebo (n=306)		
COVID-19	65 (10.7) 26.0 [20.1–33.2]	35 (11.4) 28.0 [19.5–38.9]	94 (15.5) 19.0 [15.4–23.3]	19 (7.3) 14.1 [8.5–22.1]
Nasopharyngitis	40 (6.6) 15.7 [11.2–21.4]	14 (4.6) 10.9 [5.9–18.3]	55 (9.1) 10.7 [8.0–13.9]	9 (3.4) 6.5 [2.9–12.2]
Headache	38 (6.3) 15.0 [10.6–20.6]	19 (6.2) 14.8 [8.9–23.2]	47 (7.8) 9.0 [6.6–12.0]	4 (1.5) 2.8 [0.8–7.3]
Petechiae	23 (3.8) 8.9 [5.7–13.4]	1 (0.3) 0.8 [0.0–4.2]	24 (4.0) 4.5 [2.9–6.7]	7 (2.7) 5.0 [2.0–10.4]
Urinary tract infection	19 (3.1) 7.3 [4.4–11.4]	8 (2.6) 6.1 [2.6–12.1]	28 (4.6) 5.2 [3.5–7.6]	4 (1.5) 2.8 [0.8–7.3]
Urticaria	15 (2.5) 5.7 [3.2–9.5]	15 (4.9) 11.7 [6.5–19.2]	20 (3.3) 3.7 [2.3–5.7]	7 (2.7) 5.0 [2.0–10.3]

A patient with multiple occurrences of an AE under one treatment is counted only once in this AE category for that treatment. Preferred terms are sorted in descending frequency of AE according to the double-blind remibrutinib 25 mg BID column. MedDRA Version 26.1 has been used for the reporting of AEs.

AE, adverse event; BID, twice daily; CI, confidence interval; COVID-19, coronavirus disease 2019; EAIR, exposure-adjusted incidence rate; MedDRA, Medical Dictionary for Regulatory Activities.

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Abbreviations

AE, adverse event; BID, twice daily; BMI, body mass index; CFB, change from baseline; CI, confidence interval; COVID-19, coronavirus disease 2019; CSU, chronic spontaneous urticaria; EAIR, exposure-adjusted incidence rate; H_1-AH, H_1-antihistamine; HSS7, weekly hives severity score; ISS7, weekly itch severity score; MedDRA, Medical Dictionary for Regulatory Activities; R, randomized; SAE, serious adverse event; SD, standard deviation; UAS7, weekly urticaria activity score.

Disclosures

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