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Safety of Remibrutinib in Patients with Chronic Spontaneous Urticaria: Results from the Phase 3 REMIX-1 and REMIX-2 Studies

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INTRODUCTION

- Remibrutinib is a novel, oral, highly selective Bruton's tyrosine kinase inhibitor that has demonstrated superior efficacy vs placebo and favourable safety with up to 24-weeks of treatment in the Phase 3 REMIX-1 and REMIX-2 studies in patients with chronic spontaneous urticaria (CSU) inadequately controlled by H1-antihistamines[1]
- Remibrutinib has shown a favourable safety profile and was well-tolerated in previous clinical studies,[2,3] including REMIX-1 and -2[1]

OBJECTIVE

- To report the pooled analysis of safety data up to Week 24 from final analysis of the Phase 3 REMIX studies in patients with CSU receiving remibrutinib 25 mg twice daily (bid)

METHODS

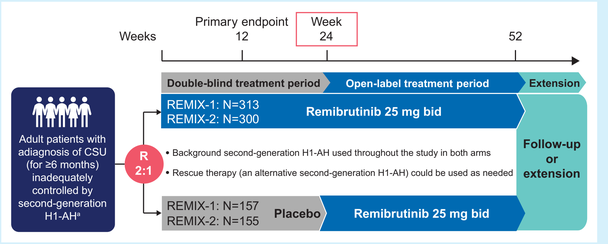
Study design

- REMIX-1 and REMIX-2 are two identical, global, double-blind, placebo-controlled Phase 3 studies (**Figure 1**). Adult patients with CSU inadequately controlled by second-generation antihistamines were randomised 2:1 to oral remibrutinib 25 mg bid or placebo for 24 weeks, followed by an open-label treatment with remibrutinib 25 mg bid for 28 weeks (patients on placebo transitioned to remibrutinib at Week 24)

Study assessments and data analysis

- Safety assessments comprised adverse events (AEs), serious AEs (SAEs), and laboratory parameters (all data presented as remibrutinib vs placebo)
- Data were analyzed using summary statistics

Figure 1. Study design[1]



AH, antihistamine; bid, twice daily; CSU, chronic spontaneous urticaria; H1, histamine 1; HSS7, weekly Hives Severity Score; ISS7, weekly Itch Severity Score; N, number of randomized patients; R, randomisation; UAS7, weekly Urticaria Activity Score.

[a]Presence of itch and hives for ≥6 consecutive weeks prior to screening despite the use of a second-generation H1-antihistamines; UAS7 score ≥16, ISS7 score ≥6, and HSS7 score ≥6 during the 7 days prior to randomization (day 1).

RESULTS

- This pooled safety analysis included randomised patients who received at least one dose of remibrutinib 25 mg bid (N=606) or placebo (N=306) for 24 weeks in the REMIX-1 & 2 studies
- Patient demographics and baseline disease characteristics were well-balanced between remibrutinib and placebo in both REMIX studies (**Table 1**)

Table 1. Patient demographics and baseline characteristics

	Pooled REMIX-1 and REMIX-2	
Patient demographics[a]	Remibrutinib 25 mg bid (n=606)	Placebo (n=306)
Age (years), mean±SD	**43.3**±14.4	**43.7**±14.1
Female, n (%)	403 (**66.5**)	204 (**66.7**)
Duration of CSU (years), mean±SD	**6.2**±8.6	**5.3**±6.7
UAS7, mean±SD	**30.6**±7.8	**29.7**±7.6
Previous experience of angioedema, n (%)	313 (**51.7**)	135 (**44.1**)
Previous exposure to anti-IgE biologics, n (%)	187 (**30.9**)	98 (**32.0**)

bid, twice daily; CSU, chronic spontaneous urticaria; IgE, immunoglobulin E; SD, standard deviation; UAS7, weekly Urticaria Activity Score.

[a]Safety set.

- During the 24-week double-blind period, the duration of treatment exposure, percentage of AEs, SAEs and AEs leading to treatment discontinuation were comparable between remibrutinib and placebo groups **(Table 2)**
- No SAE was considered related to study medication
- AEs were predominantly mild or moderate with severe AEs reported in 2.8% of patients from remibrutinib and 2.3% from placebo groups

Table 2. Overview of safety from 24-week double-blind period

	Pooled REMIX-1 and REMIX-2	
	Remibrutinib 25 mg bid (n=606), n (%)[a,b]	Placebo (n=306), n (%)[a,b]
Median exposure, Weeks	**24**	**24**
Overall AEs[c]	393 (**64.9**)	198 (**64.7**)
Serious AEs[d]	20 (**3.3**)	7 (**2.3**)
AEs leading to treatment discontinuation	17 (**2.8**)	9 (**2.9**)
AEs leading to treatment interruption	47 (**7.8**)	27 (**8.8**)
Severe AEs	17 (**2.8**)	7 (**2.3**)
Death	0	0

AE, adverse event; bid, twice daily; N, number of patients in each treatment arm; n, number of patients with at least one event.

[a]Safety set. [b]Number of patients experiencing ≥1 event. [c]Overall AEs include infection AEs. [d]Vast majority met seriousness criterion of hospitalization; no deaths were reported.

Most common AEs

- Most common AEs by system organ class (SOC) and preferred term (PT) were generally comparable between remibrutinib and placebo groups **(Table 3)**
- Infections were the most commonly reported AEs, primarily those affecting respiratory tract – COVID-19 (studies conducted during COVID-19 pandemic) and nasopharyngitis
- Petechiae (3.8% vs 0.3%) and nasopharyngitis (6.6% vs 4.6%) were more frequent with remibrutinib, and urticaria (representing CSU exacerbations, 2.5% vs 4.9%) was more common in the placebo group
  - Petechia and, similarly, AEs of purpura and ecchymosis (both reported in < 3% of patients in any treatment group), were all mild or moderate in severity and, when seen, tended to occur early on treatment (within first 3 months)
- Newly occurring liver transaminase (ALT or AST) elevations were balanced between remibrutinib and placebo during the double-blind treatment period (**Table 4**)
- All observed liver transaminase (ALT or AST) elevations across both studies were asymptomatic and transient/reversible

Table 3. Most common (≥10%) AEs with remibrutinib treatment by SOC ≥10% and/or PT ≥3% in any treatment group

	Pooled REMIX-1 and REMIX-2	
	Remibrutinib 25 mg bid (n=606), n (%)[a]	Placebo (n=306), n (%)[a]
Most frequent AEs (SOC≥10% and/or PT≥3% in any treatment group)		
Infections and infestations	**202 (33.3)**	**104 (34.0)**
COVID-19	65 (10.7)	35 (11.4)
Nasopharyngitis	40 (6.6)	14 (4.6)
Urinary tract infection	19 (3.1)	8 (2.6)
Skin and subcutaneous tissue disorders	**100 (16.5)**	**44 (14.4)**
Petechiae	23 (3.8)	1 (0.3)
Urticaria	15 (2.5)	15 (4.9)
Gastrointestinal disorders	**69 (11.4)**	**32 (10.5)**
Investigations[b]	**68 (11.2)**	**40 (13.1)**
Nervous system disorders	**59 (9.7)**	**27 (8.8)**
Headache	38 (6.3)	19 (6.2)

AE, adverse event; bid, twice daily; PT, preferred term; SOC, system organ class.

[a]Safety set. [b]These include AEs representing lab finding.

Table 4. Newly occurring liver transaminase elevations[a]

	Pooled REMIX-1 and REMIX-2	
	Remibrutinib 25 mg bid (n=606), n (%)[b]	Placebo (n=306), n (%)[b]
ALT or AST >3x ULN	**8 (1.3)**	**4 (1.3)**
ALT or AST >20x ULN	0	0
ALT or AST >3x ULN and TBL >2x ULN (Biochemical Hy's Law)	0	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase; bid, twice daily; TBL, total bilirubin levels; ULN, upper limit of normal.

[a]All were asymptomatic and transient/reversible. [b]Safety set.

CONCLUSIONS

- In the pivotal REMIX studies, remibrutinib showed favourable safety and tolerability with up to 24 weeks of treatment, consistent with the known safety profile
- Remibrutinib has the potential to become a well-tolerated novel oral treatment option for patients with CSU inadequately controlled by second-generation H1-antihistamines

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