Remibrutinib (LOU064) showed good stability of response in patients with chronic spontaneous urticaria: A novel exploratory analysis of data from the Phase 2b study

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Introduction

- Chronic spontaneous urticaria (CSU) is characterised by recurrent wheals (hives) and/or angioedema for more than 6 weeks and can have a major impact on patients' well-being[1]
- Remibrutinib (LOU064) is an oral, highly selective Bruton's tyrosine kinase (BTK) inhibitor that offers fast disease control in patients with CSU who remain symptomatic despite treatment with second-generation H_1-antihistamines.[2] It is currently in Phase 3 development for the treatment of CSU (REMIX-1: NCT05030311, REMIX-2: NCT05032157)[3,4]
- Remibrutinib showed clinical efficacy and a favourable safety profile for up to 12 weeks in the Phase 2b study (NCT03926611) and up to 52 weeks in the open-label Phase 2b extension study (NCT04109313) in patients with CSU inadequately controlled by H_1-antihistamines[5,6]

Objective

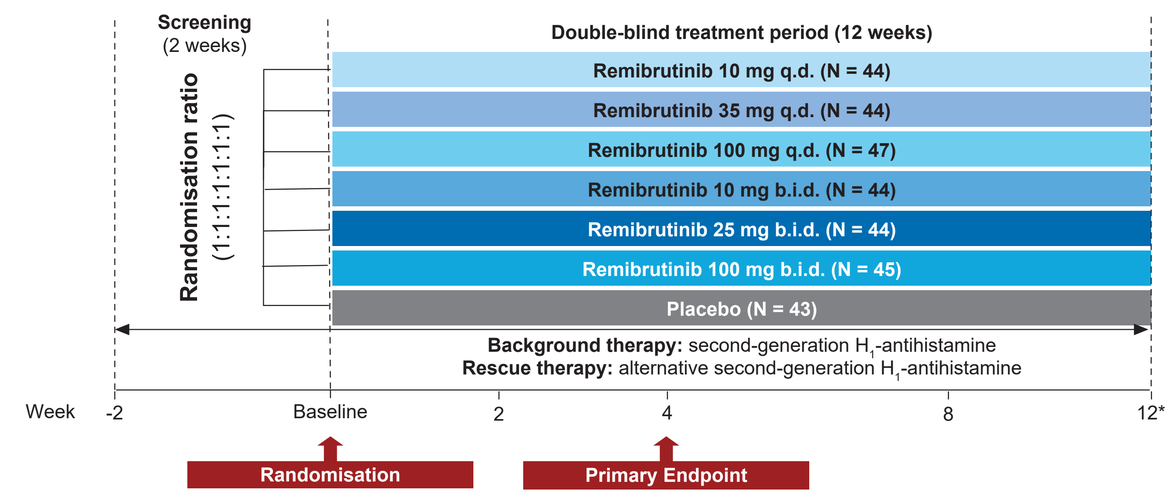
- To explore the stability of response to remibrutinib during the 12-week treatment period in the Phase 2b study

Methods

Study Design and Patients

- This was a dose-finding, multicentre, randomised, double-blind, placebo-controlled Phase 2b study (NCT03926611) conducted at 82 sites in 17 countries in patients with CSU (**Figure 1**)[5]
  - Patients were equally randomised to receive remibrutinib 10 mg once daily (q.d.), 35 mg q.d., 100 mg q.d., 10 mg twice daily (b.i.d.), 25 mg b.i.d., 100 mg b.i.d., or placebo
- Patients received second-generation H_1-antihistamines at a locally approved licensed dose and posology as background therapy throughout the study[5]

Figure 1. Study design[5]



*Eligible patients rolled over into an extension study at Week 12 or at Week 16, following roll-over criteria defined in the extension study protocol and dependent on ECHA approval from participating countries. Background therapy was a second-generation H_1-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 second-generation H_1-antihistamine at a locally approved licensed posology that differed from the background H_1-antihistamine, is 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: ECHA, European Chemical Agency: mg, milligrams: N, number of patients randomised in each group; q.d, once daily.

Study assessments

- The rates of patients experiencing worsening episodes, the duration of worsening episode, and the time to first worsening episode during the treatment period were assessed
- A worsening episode was defined as a temporary increase of rolling weekly Urticaria Activity Score (rUAS7) ≥10 (based on minimal clinically important difference for UAS7) from the lowest rUAS7 achieved before the episode
- The end of the worsening episode was defined as the day, when rUAS7 dropped back to <10 points above the initial lowest rUAS7 before the episode
- The rUAS7 was calculated as the UAS7 for every possible set of 7 consecutive days across the study treatment period
- The number of days, including the first day, spent with a worsening episode was calculated as the duration of the worsening episode
  - Patients with at least one worsening episode were considered for this analysis
- Patients captured their daily UAS in an e-diary

Results

- Patient demographics and baseline disease characteristics in patients without any worsening episode and in patients with at least one worsening episode are presented in **Table 1**
- The duration of CSU was observed to be higher in patients with at least one worsening episode versus those without any worsening episode (**Table 1**)

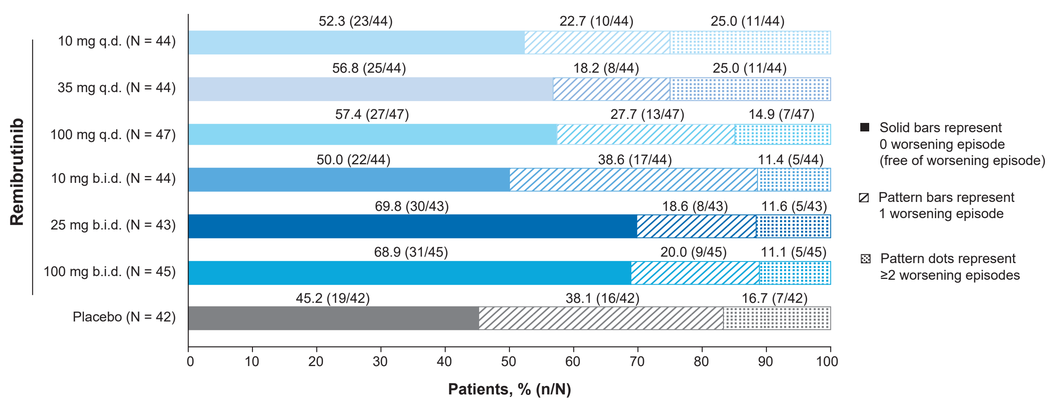
Table 1. Patient demographics and baseline disease characteristics

Phase 2b Core Study															
	Patients with at least one worsening episode in treatment phase								Patients without any worsening episodes in treatment phase							
	Remibrutinib						Placebo	Total	Remibrutinib						Placebo	Total
Baseline characteristics	10 mg q.d. n = 21	35 mg q.d. n = 19	100 mg q.d. n = 20	10 mg b.i.d. n = 22	25 mg b.i.d. n = 13	100 mg b.i.d. n = 14	n = 23	N = 132	10 mg q.d. n = 23	35 mg q.d. n = 25	100 mg q.d. n = 27	10 mg b.i.d. n = 22	25 mg b.i.d. n = 30	100 mg b.i.d. n = 31	n=19	N = 177
Age (years)	36.5 ± 14.7	43.8 ± 16.8	43.0 ± 9.8	43.7 ± 16.4	50.6 ± 13.9	46.6 ± 13.0	42.8 ± 13.6	43.3 ± 14.5	47.9 ± 15.5	44.2 ± 16.6	46.9 ± 15.5	48.5 ± 13.9	47.0 ± 14.2	44.1 ± 14.2	47.3 ± 17.2	46.4 ± 15.1
Female, n (%)	16 (76.2)	14 (73.7)	17 (85.0)	16 (72.7)	11 (84.6)	13 (92.9)	16 (69.6)	103 (78.0)	19 (82.6)	16 (64.0)	22 (81.5)	16 (72.7)	21 (70.0)	16 (51.6)	8 (42.1)	118 (66.7)
Weight (kg)	78.2 ± 22.4	86.4 ± 21.9	77.4 ± 15.7	76.3 ± 17.8	70.8 ± 17.2	77.7 ± 15.1	80.8 ± 18.6	78.6 ± 18.8	78.5 ± 16.8	73.4 ± 17.2	76.2 ± 14.1	80.5 ± 15.9	80.2 ± 20.8	79.6 ± 21.2	75.6 ± 14.0	77.8 ± 17.6
Duration of CSU (years)	6.4 ± 5.3	7.0 ± 10.7	4.4 ± 5.6	4.5 ± 5.1	5.4 ± 7.2	9.4 ± 6.5	3.5 ± 4.4	5.6 ± 6.6	6.0 ± 9.5	5.0 ± 7.3	5.9 ± 6.0	5.2 ± 5.9	3.1 ± 2.7	2.3 ± 2.3	3.6 ± 5.4	4.3 ± 5.9
Angioedema positivity, n (%)	11 (52.4)	9 (47.4)	12 (60.0)	13 (59.1)	5 (38.5)	10 (71.4)	13 (56.5)	73 (55.3)	15 (65.2)	20 (80.0)	15 (55.6)	15 (68.2)	17 (56.7)	13 (41.9)	9 (47.4)	104 (58.8)
CU index positivity, n (%)	7 (33.3)	8 (42.1)	6 (30.0)	4 (18.2)	3 (23.1)	5 (35.7)	9 (39.1)	42 (31.8)	9 (39.1)	11 (44.0)	12 (44.4)	11 (50.0)	8 (26.7)	9 (29.0)	5 (26.3)	65 (36.7)
Baseline UAS7 score	31.9 ± 6.6	32.7 ± 6.6	27.7 ± 6.5	29.4 ± 6.1	27.0 ± 9.2	30.6 ± 5.9	26.6 ± 7.1	29.4 ± 7.0	31.0 ± 7.6	30.1 ±7.6	29.1 ± 7.4	30.3 ± 7.4	30.3 ± 7.3	28.7 ± 6.0	29.1 ± 8.3	29.8 ± 7.2
Baseline DLQI score	17.0 ± 6.2	11.2 ± 5.8	12.4 ± 7.5	12.3 ± 6.1	12.8 ± 8.9	12.4 ± 6.8	14.2 ± 7.8	13.3 ± 7.1	12.8 ± 7.4	13.8 ± 7.0	12.8 ± 7.0	13.0 ± 6.5	12.9 ± 5.5	10.0 ± 6.6	12.3 ± 8.1	12.5 ± 6.8

Data are presented as mean±SD, unless stated otherwise. b.i.d., twice daily; CSU, chronic spontaneous urticaria; CU, chronic urticaria; DLQI, dermatology life quality index; n, number of patients; N, total number of patients; q.d., once a day; SD, standard deviation; UAS7, weekly Urticaria Activity Score.

- During the treatment period, a higher proportion of patients were free of worsening episodes across remibrutinib doses (range: 50.0% to 69.8% vs placebo [45.2%]) (**Figure 2**)

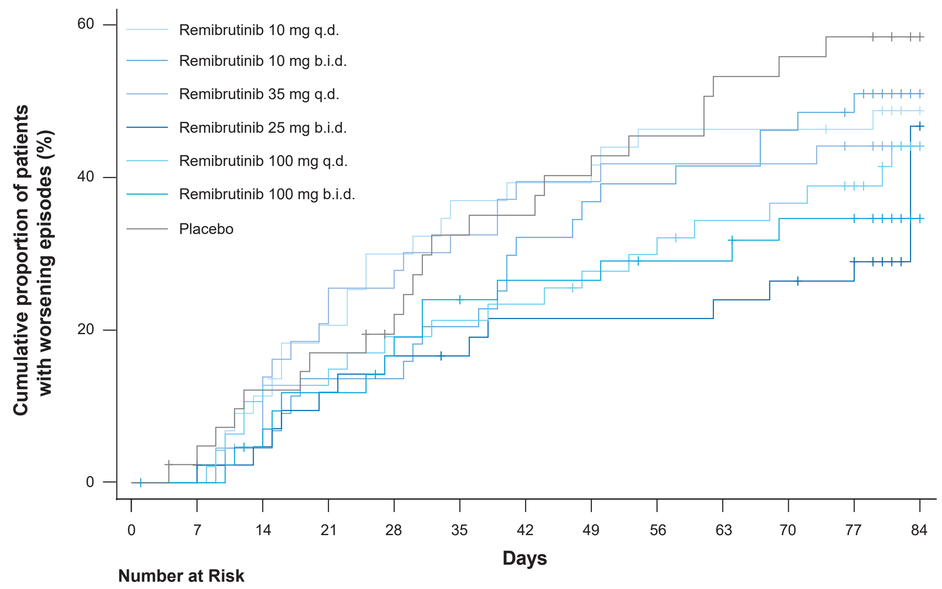
Figure 2. Percentage of patients experiencing number of worsening episodes based on rUAS7, by treatment group, during 12-week study treatment (full analysis set)



b.i.d., twice daily; N, total number of patients in each arm; n, number of patients experiencing number of worsening episodes based rUAS7; q.d., once daily; rUAS7, rolling weekly Urticaria Activity Score.

- The cumulative proportion of patients with time to first worsening episodes over 12 weeks is presented in **Figure 3**
- The median (95% confidence interval) time to first worsening episode was not reached across remibrutinib arms (except 10 mg b.i.d. 77.0 days [47.0, not applicable {NA}]) versus placebo (61.0 days [36.0, NA])

Figure 3. Time to first worsening episode based on rUAS7 in the treatment period (full analysis set)



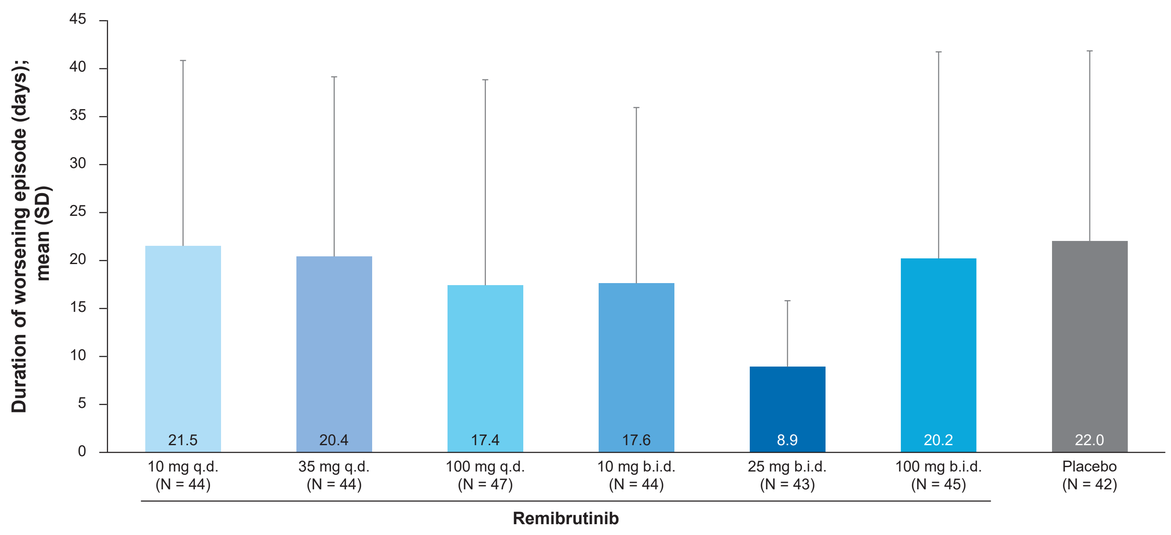
Number at Risk

Remibrutinib 10 mg q.d.	44	44	39	34	30	27	26	26	23	23	23	22	6
Remibrutinib 35 mg q.d.	44	44	41	34	32	29	26	26	25	25	25	23	5
Remibrutinib 100 mg q.d.	47	47	42	41	38	37	36	33	32	29	28	26	4
Remibrutinib 10 mg b.i.d.	44	44	42	38	38	34	29	27	26	25	23	21	3
Remibrutinib 25 mg b.i.d.	43	43	40	37	35	34	32	32	32	31	30	29	3
Remibrutinib 100 mg b.i.d.	44	43	40	37	34	31	29	29	26	26	23	23	3
Placebo	42	40	36	34	31	26	25	23	21	18	17	16	4

b.i.d., twice daily; q.d., once daily; rUAS7, rolling weekly Urticaria Activity Score.

- The mean (standard deviation [SD]) duration of worsening episode across remibrutinib doses ranged from 8.9 (6.9) to 21.5 (19.3) days and placebo 22.0 (19.8) days (**Figure 4**)
- The mean (SD) duration of worsening episode was shortest with remibrutinib 25 mg b.i.d. over 12 weeks

Figure 4. Duration of worsening episode based on rUAS7 (full analysis set)*



*Only patients with at least one worsening episode were considered for this analysis.

b.i.d., twice daily; N, total number of patients; q.d., once daily; rUAS7, rolling weekly Urticaria Activity Score.

Conclusions

- This exploratory analysis from the Phase 2b study showed more patients free of urticaria worsening in all remibrutinib treatment arms compared with placebo
- The time to first worsening episode was delayed and the duration of worsening episode was decreased with remibrutinib
- The treatment response with remibrutinib remained stable during the study, which was shown to have a favourable impact on patients' dermatology quality of life[7]

References

1. Zuberbier T, et al. *Allergy.* 2022;77(3):734–766
2. Angst D, et al. *J Med Chem.* 2020;63:5102–5118
3. ClinicalTrial.gov.in. NCT05030311. Accessed on 28th April 2023
4. ClinicalTrial.gov.in. NCT05032157. Accessed on 28th April 2023
5. Maurer M, et al. *J Allergy Clin Immunol.* 2022;150(6):1498–1506.e2
6. Carr W, et al. AAAAI 2023 (Oral Presentation 3611 - Late-breaker)
7. Bernstein JA, et al. AAD 2022 (Poster presentation 33586)

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