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

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1 Disclosures and acknowledgements

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  - Artem Zharkov is an employee of Novartis Pharma AG, Basel, Switzerland

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2 Introduction and study objective

- **Chronic spontaneous urticaria (CSU)** is characterised 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 an oral, highly selective BTK inhibitor** that offers fast disease control in patients with CSU patients who remain symptomatic despite second-generation H_1-antihistamines[2]
- In the preceding core Phase 2b dose-finding study (NCT03926611), remibrutinib showed **clinical efficacy** and a **favourable safety profile** over up to 12 weeks of treatment in patients with **moderate to severe CSU** inadequately controlled by H_1-antihistamines[3]
- Here, we report the **final 52-week** data from the Phase 2b extension study

Objective

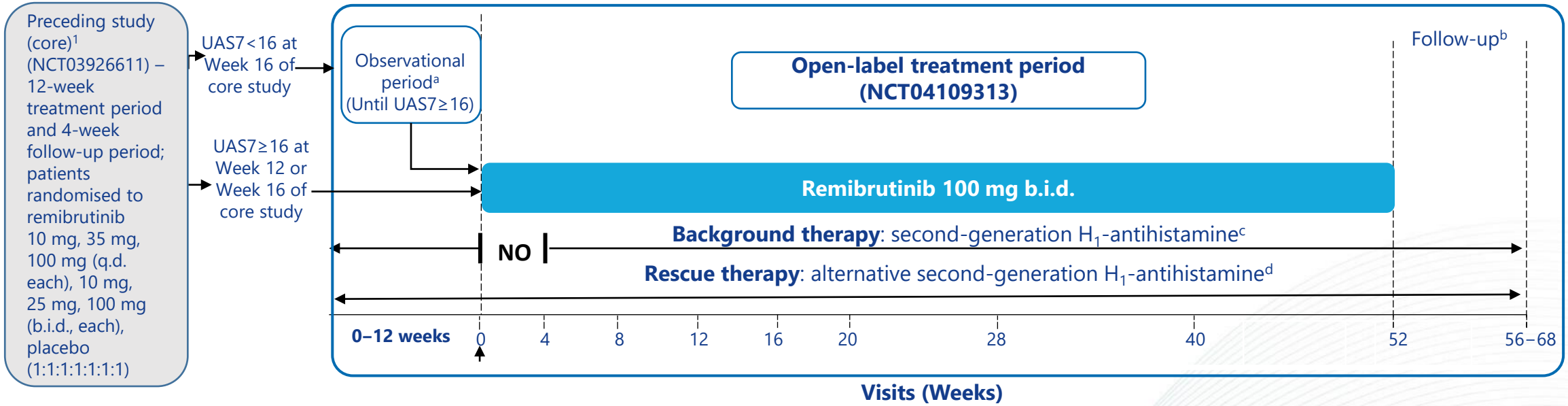
To evaluate the long-term safety, tolerability, and efficacy of remibrutinib in patients with CSU in the open-label extension study

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

1. Zuberbier T, et al. *Allergy*. 2022;77(3):734–766; 2. Angst D, et al. J Med Chem. 2020;63:5102–5118;
3. Maurer M, et al. *J Allergy Clin Immunol.* 2022 Dec;150(6):1498–1506.e2.

3 Study design

52-week long-term open-label extension study of patients who completed the preceding core study[1-3]



[a]Patients who never relapsed (UAS7≥16 at least once) within 12 weeks completed the study at the end of the observational period.
[b]The minimum duration of the follow-up period was 4 weeks for all subjects who stopped treatment with remibrutinib. Patients who achieved a UAS7≤6 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.
[c]Background therapy was a second-generation H_1-antihistamine at a locally approved licensed posology given with a stable treatment regimen. Administration of background H_1-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.
[d]Rescue therapy was a second-generation H_1-antihistamine at a locally approved licensed posology that was eliminated primarily via renal excretion. The rescue H_1-antihistamine used differed from the background H_1-antihistamine and was only given to treat unbearable symptoms (itch) of CSU on a day-to-day basis.
b.i.d., twice daily; N, total number of patients; q.d., once daily; UAS7, weekly Urticaria Activity Score
1. Maurer M, et al. J Allergy Clin Immunol. 2022 Dec;150(6):1498–1506.e2; 2. Giménez-Arnau A, et al. Poster presented at EADV 2022, 07–11 September 2022, Milan, Italy; #P1722; 3. Giménez-Arnau A, et al. Oral presentation at EAACI 2022, 01–03 July 2022, Prague, Czech Republic.

3 Study eligibility, outcomes and statistical analysis

Study eligibility

- Patients who completed the core study according to protocol

Study outcomes

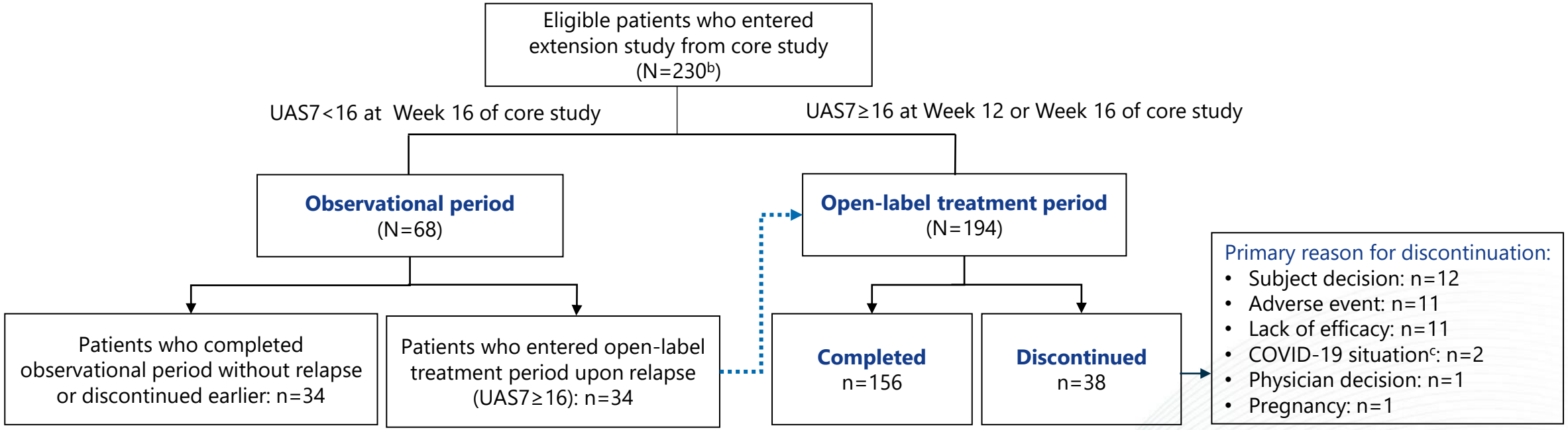
- The primary objective included occurrence of treatment-emergent adverse events
- Other outcomes of interest included change from baseline in UAS7 and proportion of patients with a complete response to treatment (UAS7=0) at Week 2 and 52

Statistical analysis

- Treatment-emergent adverse events were summarised as grouped (by primary system organ class) and as individual (by preferred term) events
- Change from baseline in UAS7 and proportion of patients achieving UAS7=0 at Week 2 and Week 52 were analysed using summary statistics

UAS7, weekly Urticaria Activity Score.

4 Approximately 80% of patients completed the full 52-week treatment period[a]



- Of 230 patients enrolled in the study, **68 patients (29.6%)** entered the **observational period** (UAS7<16), of which 34 patients rolled over into treatment period
- Overall, **194 patients (84.3%)** entered the **treatment period** either via the observational period or directly from Week 12 or Week 16 of the core study, depending on their UAS7 score, and received at least one dose of remibrutinib 100 mg b.i.d.

[a]Study was conducted mostly during the COVID-19 pandemic phase; FPFV: 24 Oct 2019; LPLV: 09 Sep 2022
[b]Of the 230 patients who enrolled in the extension study, 1 patient failed at screening, and another patient entered the treatment period but did not receive the study treatment.
[c]All reasons with the term COVID-19 term are included in COVID-19 situation category.
b.i.d., twice daily; FPFV, first patient first visit; LPLV, last patient last visit, N, total number of patients; n, number of patients in each category; UAS7, weekly Urticaria Activity Score.

4 Patient demographics and baseline characteristics in the extension study were comparable to that of the core study

Characteristics	Extension study*	Core study[1#]
	Remibrutinib 100 mg b.i.d. (N=194)	Total Randomised (N=311)
Age (years)	45.5±14.12	45.0±14.90
Gender (female), n (%)	139 (71.6)	222 (71.4)
Weight (kg)	77.8±17.86	78.1±18.03
Duration of CSU (years)	5.8±6.68	4.9±6.23
UAS7 score	27.9±8.23	29.6±7.13
Previous exposure to anti-IgE therapy, n (%)	54 (27.8)	84 (27.0)

Data are expressed as mean±SD unless stated otherwise.
*Safety set; #Randomised set.
b.i.d., twice daily; CSU, chronic spontaneous urticaria; IgE, immunoglobulin E; n, number of patients randomised to each arm; N, total number of patients; SD, standard deviation; UAS7, weekly Urticaria Activity Score.
1. Maurer M, et al. *J Allergy Clin Immunol.* 2022 Dec;150(6):1498–1506.e2.

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

Overall safety profile Patients, n (%)	Extension study*	Core study*	
	Remibrutinib 100 mg b.i.d. (N=194)	Remibrutinib any dose (n=267)	Placebo (n=42)
Duration of exposure, median (Q1–Q3) [weeks]	52.1 (51.6–52.4)	12.1 (12.0–12.3)	12.1 (12.1–12.7)
Patients with ≥1 TEAE	139 (71.6)	155 (58.1)[1]	18 (42.9)[1]
Discontinued study treatment due to TEAE(s)	11 (5.7)	7 (2.6)[1]	0 (0.0)[1]
Patients with SAE(s)	6 (3.1)	5 (1.9)[1]	0 (0.0)[1]
Death	0 (0.0)	0 (0.0)[1]	0 (0.0)[1]

- Overall, 71.6% (139/194) of patients reported ≥1 TEAE with remibrutinib 100 mg b.i.d. in the extension study; the majority were mild-to-moderate with 35.1% (68/194) of patients reporting at least one mild or moderate (32.5%, 63/194) TEAE; severe events were reported in 4.1% (8/194) of patients
- 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[1]
- No deaths occurred during the core[1] 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 >3× and <5×ULN with normal bilirubin levels; both returned to normal levels during the study and did not require treatment modification

Here we report TEAEs and SAEs only. MedDRA version 24.0 was used for reporting.
*Safety set
AE, adverse event; ALT, alanine aminotransferase; b.i.d., twice a day; 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 of normal.
1. Maurer M, et al. *J Allergy Clin Immunol.* 2022 Dec;150(6):1498–1506.e2.

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

Safety events Patients, n (%)	Extension study*	Core study*	
	Remibrutinib 100 mg b.i.d. (N=194)	Remibrutinib any dose (n=267)	Placebo (n=42)
Top 3 grouped events by SOC in the 100 mg b.i.d. group in the extension study			
Infections and infestations	60 (30.9)	64 (24.0)[1]	9 (21.4)[1]
Skin and subcutaneous tissue disorders	52 (26.8)	45 (16.9)[1]	2 (4.8)[1]
Gastrointestinal diseases	32 (16.5)	30 (11.2)	5 (11.9)
Top 5 events by preferred term in the 100 mg b.i.d. group in the extension study or any remibrutinib dose or placebo group in the core study			
CSU	22 (11.3)	16 (6.0)[1]	1 (2.4)
COVID-19	16 (8.2)	3 (1.1)	1 (2.4)
Headache	13 (6.7)	26 (9.7)[1]	6 (14.3)
Eczema	10 (5.2)	2 (0.7)	0 (0.0)
Nasopharyngitis	8 (4.1)	23 (8.6)[1]	3 (7.1)

- Infections were mostly mild-to-moderate, primarily infections of the upper respiratory tract (as study was mostly conducted during COVID-19 pandemic)
- The higher rate of grouped skin and subcutaneous tissue disorder events was driven by events of CSU (11.3% in patients in the extension study, of which 76% of events occurred on or after the last treatment day)
  - CSU events in the core study in remibrutinib arm were also primarily seen in the treatment-free follow-up period
- 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
*Safety set.
b.i.d., twice daily; CSU, chronic spontaneous urticaria; COVID-19, coronavirus disease; I
MedDRA, Medical Dictionary for Regulatory Activities; N, total number of patients; n, number of patients; SOC, system organ class.
1. Maurer M, et al. *J Allergy Clin Immunol.* 2022 Dec;150(6):1498–1506.e2.

4 Minor cutaneous bleedings and cytopenias remained stable with long-term treatment with remibrutinib

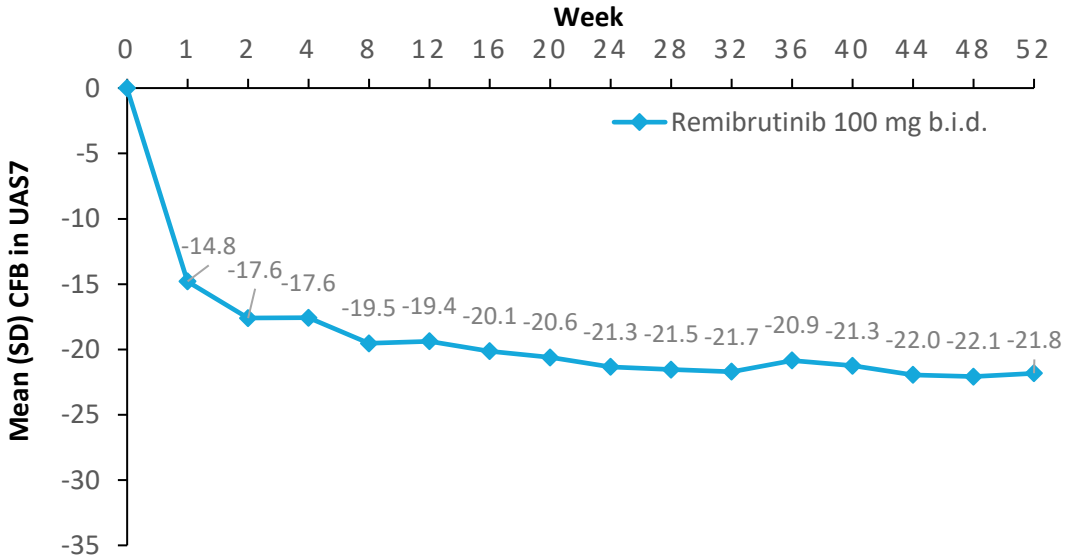
Incidence, n (%)	Extension study*	Core study*	
	Remibrutinib 100 mg b.i.d. (N=194)	Remibrutinib any dose (n=267)	Placebo (n=42)
Bleeding (platelet dysfunction)	12 (6.2)	18 (6.7)	1 (2.4)
Cytopenias (including neutropenia and lymphopenia)	2 (1.0)	8 (3.0)	1 (2.4)

- All reported bleeding events were minor and mild-to-moderate in nature, primarily cutaneous (e.g. petechia, purpura) events
- All cytopenias were mild in severity
- Cytopenias continued to be rare with long-term treatment and were not correlated with infectious events

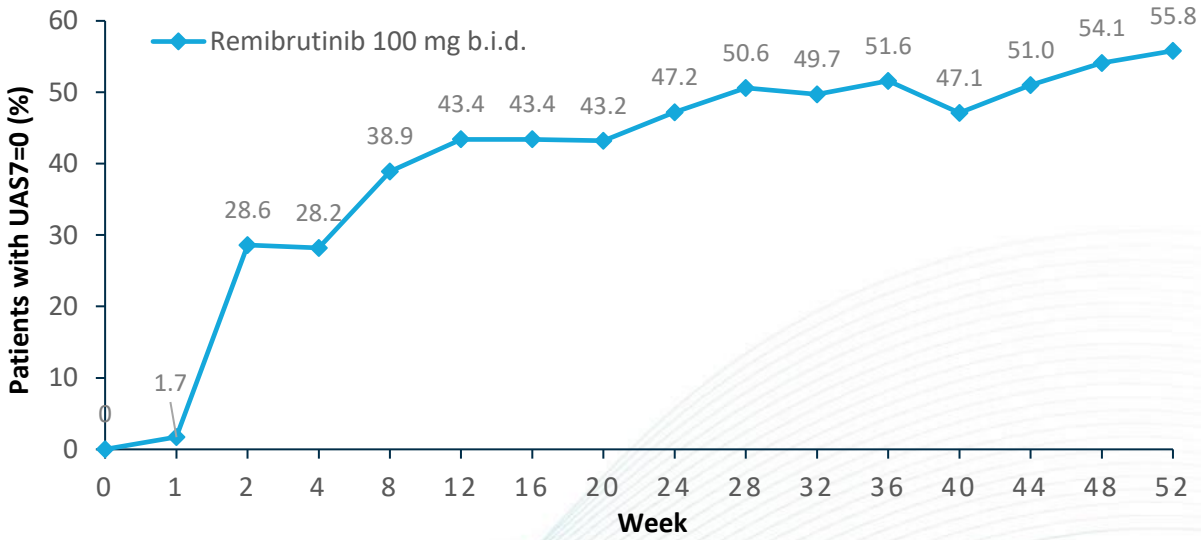
MedDRA version 24.0 was used for reporting.
*Safety set.
b.i.d., twice daily; MedDRA, Medical Dictionary for Regulatory Activities; N, total number of patients; n, number of patients in each arm.

4 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

Change from baseline in UAS7 during treatment period (as observed; Safety set)



UAS7=0 response rate over time during treatment period (as observed; Safety set)



- At Week 2 and Week 52, the mean change from baseline in UAS7 with remibrutinib 100 mg b.i.d. was -17.6 and −21.8, respectively
- The percentage of patients achieving UAS7=0 increased during the study, with 28.6% and 55.8% of patients achieving UAS7=0 at Week 2 and Week 52, respectively

b.i.d., twice daily; CFB, change from baseline; SD, standard deviation; UAS7, weekly Urticaria Activity Score

5 Conclusions

- The final analysis from the Phase 2b extension study showed a **favourable 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 that in 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)

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

1. Maurer M, et al. *J Allergy Clin Immunol.* 2022 Dec;150(6):1498–1506.e2; 2. Giménez-Arnau A, et al. European Academy of Allergy and Clinical Immunology (EAACI), 2022 Congress, 09–11 June 2023 June 2023, Hamburg, Germany. Abstract # 000831.

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