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Remibrutinib, a BTKi, Has No Impact on Serum Immunoglobulin Levels: Insights From Chronic Spontaneous Urticaria

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Introduction

- Remibrutinib is a novel, highly selective and potent, covalent, oral Bruton's tyrosine kinase inhibitor that downregulates myeloid and B-cell activation without depleting B cells[1,2]
- The ongoing remibrutinib clinical development programme comprises >25 studies, with >2900 subjects exposed to remibrutinib at doses up to 600 mg/day and duration of up to 52 weeks[3]
- Remibrutinib has demonstrated efficacy with favourable safety profile for up to 52 weeks, including with 100 mg twice daily (b.i.d.) dose, in the phase 2b core and extension studies (NCT03926611 and NCT04109313, respectively) and in the 24-week primary analysis of the phase 3 studies (REMIX-1: NCT05030311, REMIX-2: NCT05032157) in patients with chronic spontaneous urticaria (CSU)[4–7]
- Remibrutinib is currently being evaluated in two pivotal phase 3 trials in multiple sclerosis (MS), REMODEL-1 (NCT05147220) and REMODEL-2 (NCT05156281), designed to establish the therapeutic potential of remibrutinib as a novel treatment in relapsing multiple sclerosis (RMS)[8]
- Effects on immunoglobulin levels have been observed with certain disease-modifying therapies in MS[9]

Objective: To assess the mean serum immunoglobulin levels and incidence rates of infections over time in a phase 2b core and extension study of remibrutinib in CSU, including with 100 mg b.i.d., the dosing regimen being evaluated in the phase 3 trials in RMS

1. Angst D, et al. *J Med Chem*. 2020;63:5102–5118. **2.** Pulz R, et al. EPO0896. Poster presented at the 38th congress of the ECTRIMS; 26–28 October 2022; Amsterdam, the Netherlands. **3.** Data on file. Investigator brochure. Novartis Pharma AG; 10 March 2024. **4.** Maurer M, et al. *J Allergy Clin Immunol*. 2022;150:1498–1506.e2. **5.** Jain V, et al. *J Allergy Clin Immunol*. 2024;153:479–486.e4. **6.** Saini S, et al. LB001 – Late-breaker. Oral presentation at: ACAAI annual meeting; 9–13 November 2023; Anaheim, California, USA. **7.** McDonald C, et al. *Immunology.* 2021;164:722–736. **8.** Wiendl H, et al. P44. Poster presented at the European Charcot Foundation (ECF) 2023; 9–11 November 2023; Baveno, Italy. 9. Klein A, et al. *Ther Adv Neurol Disord*. 2023;16:17562864231162661.

b.i.d., twice daily; **CSU**, chronic spontaneous urticaria; **MS**, multiple sclerosis; **RMS**, relapsing MS.

Methods

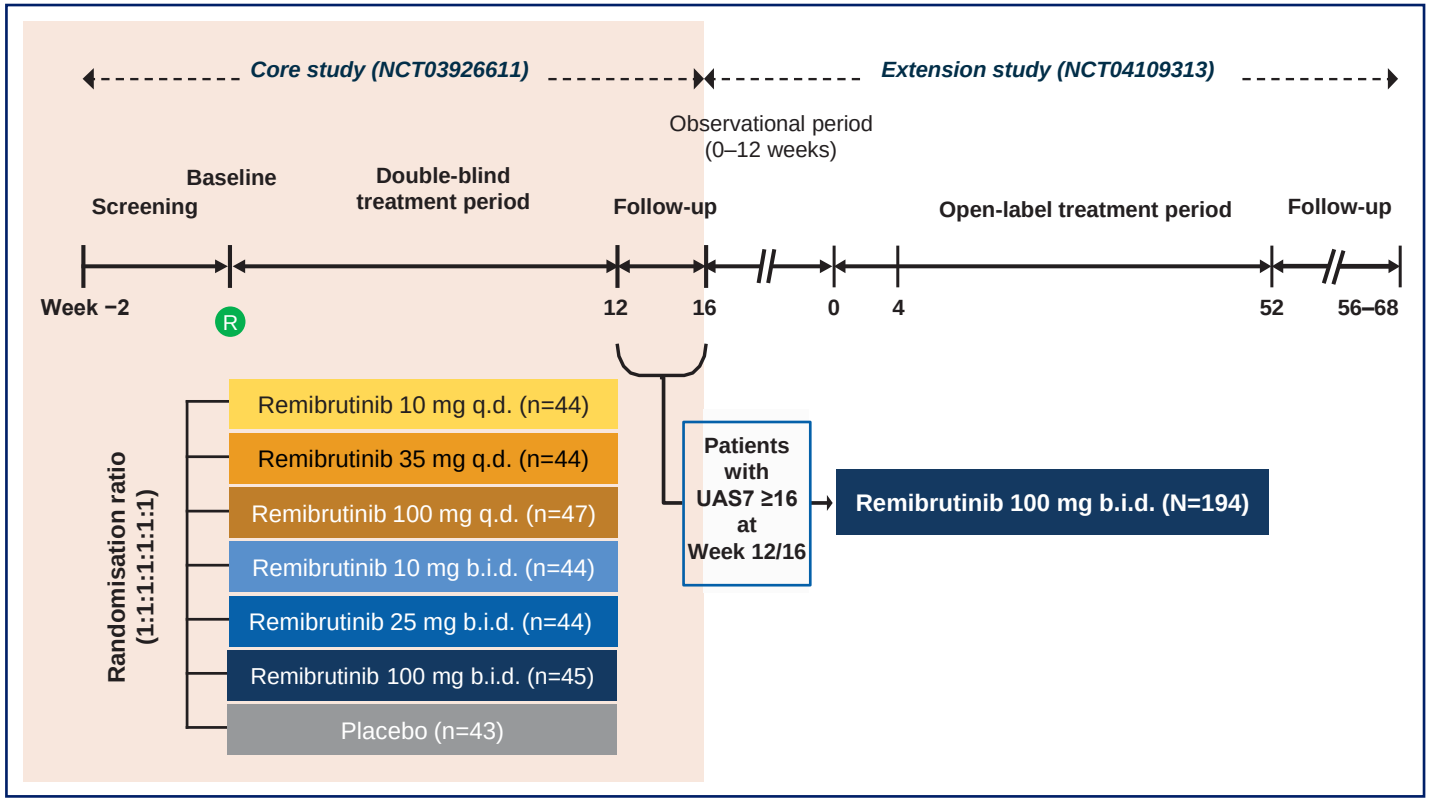
Study design and patients

- The phase 2b core study was a dose-finding, multicentre, randomised, double-blind, placebo-controlled study conducted across 17 countries in patients with CSU[1]

Study assessments and statistical analysis

- Total mean serum IgG and IgM levels were assessed at baseline and Week 12 during the core study and at baseline, Week 28, and Week 52 during the extension study
- Exposure-adjusted incidence rate (EAIR) of infections (events per 100 patient-years) and Ig levels were analysed using summary statistics based on the safety set

Figure. Study design[a]



[a]Further details on the study design are provided in reference 1 and 2. Of the 311 patients randomised in the core study, 309 were included in the full analysis and safety sets; of whom, 194 entered the extension phase.

1. Maurer M, et al. *J Allergy Clin Immunol*. 2022;150:1498–1506.e2. **2.** Jain V, et al. *J Allergy Clin Immunol*. 2024;153:479–486.e4.

b.i.d., twice daily; **CSU**, chronic spontaneous urticaria; **Ig**, immunoglobulin; **n**, number of patients included in each group; **N**, total number of patients in the extension phase; **q.d.**, once daily; **R**, randomisation; **UAS7**, weekly Urticaria Activity Score.

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Patient demographics and baseline disease characteristics (safety set)

Characteristics	Core Study		Extension Study
	Any remibrutinib arm (N=267)	Placebo (N=42)	Remibrutinib 100 mg b.i.d. (N=194)
Age, years	45.1±14.8	44.8±15.3	45.5±14.1
Female, n (%)	197 (73.8)	24 (57.1)	139 (71.6)
BMI, kg/m^2	28.1±6.1	27.2±6.4	28.1±6.2
Baseline serum Ig levels			
IgG (g/L)	10.9±2.4	10.8±2.6	11.0±2.4
IgM (g/L)	1.2±0.9	1.1±0.7	1.0±0.8

- Of the 309 patients included in the phase 2b core study, 194 patients who rolled-over to the 52-week extension study were included in the analysis
- Patient demographics, baseline disease characteristics, and mean serum IgG and IgM levels were comparable between groups in the core study and across core and extension studies

Data are represented as mean±SD unless specified otherwise.

b.i.d., twice daily; **BMI**, body mass index; **Ig**, immunoglobulin; **N**, total number of patients in each arm; **SD**, standard deviation.

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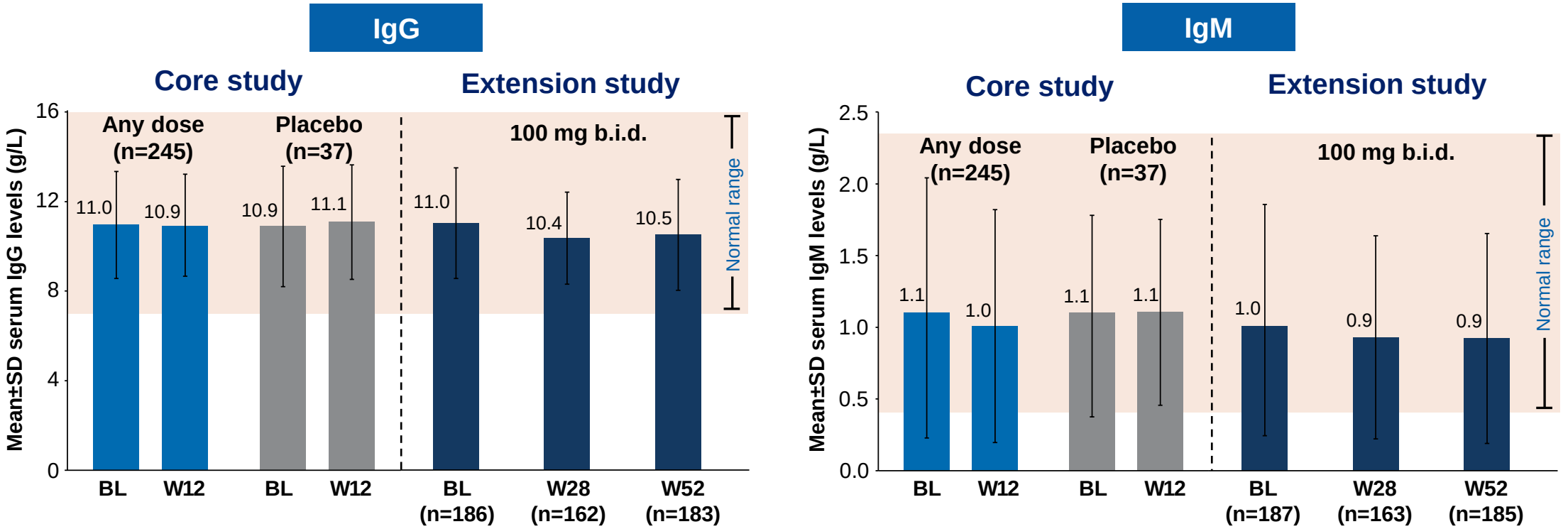
Mean serum IgG and IgM levels in the core study and the extension study (safety set) in remibrutinib and placebo arms



- No clinically meaningful change from baseline in the total mean serum IgG and IgM levels in any remibrutinib arm (any dose) was observed at Week 12 in the core study or Weeks 28 and 52 in the extension study with 100 mg b.i.d.

b.i.d., twice daily; **BL**, baseline; **Ig**, immunoglobulin; **n**, number of patients evaluated in each arm; **SD**, standard deviation; **W**, week.

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Infection rates (EAIR) in the core and extension studies (safety set)

	Core Study		Extension Study
	Any remibrutinib arm (N=267)	Placebo (N=42)	Remibrutinib 100 mg b.i.d. (N=194)
Infection rates (EAIR, 95% [CI])	107.7 (83.5–136.8)	98.7 (45.1–187.3)	40.3 (30.9–51.8)

- EAIRs of infections did not increase with long-term exposure to remibrutinib

Infections were defined as MedDRA SOC infections and infestations.

b.i.d., twice daily; **CI**, confidence interval; **EAIR**, exposure-adjusted incidence rate; **MedDRA**, Medical Dictionary for Regulatory Activities; **N**, total number of patients; **SOC**, System Organ Class.

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Conclusions

- Remibrutinib treatment had no clinically meaningful impact on total mean immunoglobulin levels in participants with CSU in phase 2 studies, including those who received long-term treatment up to 52 weeks with 100 mg b.i.d., the dose used in multiple sclerosis clinical trials
- EAIRs of infections did not increase in the extension study and remained comparable to what was observed in the core study
- The results of these analyses are in line with the favourable safety profile observed with remibrutinib across immune-mediated diseases to date

CSU, chronic spontaneous urticaria; **EAIR**, exposure-adjusted incidence rate.

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Acknowledgements

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