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Remibrutinib: A Novel BTKi in Development for MS With a Favorable Safety Profile in Various Autoimmune Disorders

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SUMMARY

1 **The safety profile of remibrutinib was explored in phase 2 clinical trials in various autoimmune disorders including chronic spontaneous urticaria, Sjögren's syndrome, and asthma**

2 **Remibrutinib demonstrated a favorable safety profile and was well tolerated at all doses studied in the phase 2 trials and in the 52-week open-label extension (up to 100 mg BID) in various autoimmune disorders**

3 **These findings support the development of remibrutinib in phase 3 clinical trials for the treatment of MS**

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INTRODUCTION

- Remibrutinib, a novel, potent, highly selective, covalent, oral Bruton's tyrosine kinase inhibitor, is currently being investigated in phase 3 trials for the treatment of multiple sclerosis (MS; NCT05147220/NCT05156281)[1]
- Remibrutinib showed a favorable selectivity and potency profile *in vitro*,[2] with the potential to minimize off-target toxicity and associated adverse events (AEs)
- The remibrutinib clinical development program includes 17 studies with >1000 participants (healthy volunteers and patients with various conditions) exposed to remibrutinib at doses ranging from 0.5 to 600 mg and with varying durations up to 52 weeks

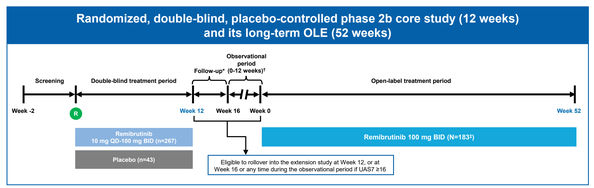
OBJECTIVE

- To present an overview of the safety of remibrutinib from phase 2 clinical trials in various autoimmune disorders

METHODS

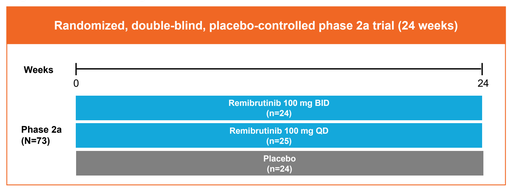
- Data from a final analysis of phase 2 trials in chronic spontaneous urticaria (CSU; NCT03926611), Sjögren's syndrome (SjS; NCT04035668), and asthma (NCT03944707), and an interim analysis of the open-label extension (OLE) in CSU (NCT04109313) were included in this analysis
- Efficacy, safety, and tolerability of remibrutinib in adult patients with CSU inadequately controlled by H_1 histamines was assessed in a multicenter, randomized, double-blind, placebo-controlled, dose-finding, phase 2 core study (NCT03926611; **Figure 1**). Patients were allocated to 1 of 7 treatment arms and received either remibrutinib 10, 35, or 100 mg once daily (QD); remibrutinib 10, 25, or 100 mg twice daily (BID); or placebo for 12 weeks
  - After 12 weeks, patients were eligible to roll over into the 52-week, single-arm OLE study (NCT04109313), where they received remibrutinib 100 mg BID (**Figure 1**)
- The LOUiSSe trial (NCT04035668) was an adaptive-design phase 2 study to establish safety and efficacy and characterize dose-response of remibrutinib in patients with moderate to severe SjS (**Figure 2**). In this 24-week study, patients were allocated to 1 of 3 treatments arms that received either remibrutinib 100 mg QD, remibrutinib 100 mg BID, or placebo
- Efficacy and safety of remibrutinib in patients with asthma were assessed via a multicenter, randomized, placebo-controlled, patient- and investigator-blinded, parallel-group trial (NCT03944707; **Figure 3**). For 12 weeks, patients received either remibrutinib 100 mg QD or placebo
- Safety assessments comprised AEs (including serious AEs [SAEs], AEs leading to treatment discontinuation, and AEs of special interest [AESIs]), vital signs, electrocardiograms (ECGs), and laboratory parameters

Figure 1. Study Designs for the Phase 2 Core and Extension Trials for Remibrutinib in CSU



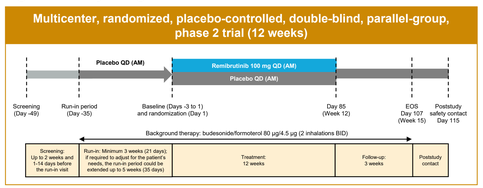
BID, twice daily; CSU, chronic spontaneous urticaria; n, number of patients included in each group; N, total number of patients; OLE, open-label extension; QD, once daily; R, randomization; UAS7, weekly Urticaria Activity Score
*Patients with UAS7 <16 at Week 12 were not eligible to roll over into the extension study but needed to enter the follow-up period of the core study; †If patients had UAS7 <16 at Week 16, they were allocated to the observational period of the extension study for up to 12 weeks. After a relapse in the extension study (UAS7 ≥16 at least once), at any time during these 12 weeks, the observational period was terminated immediately, and patients entered the open-label treatment period; ‡Data for 183 enrolled patients were available at the time of interim analysis (July 2021)

Figure 2. Study Design for LOUiSSe Trial* for Remibrutinib in SjS



BID, twice daily; n, number of patients included in each group; N, total number of patients; QD, once daily; SjS, Sjögren's syndrome
*A study of remibrutinib in SjS

Figure 3. Study Design for Phase 2 Trial for Remibrutinib in Asthma



AM, morning; BID, twice daily; EOS, end of study; QD, once daily

RESULTS

- A total of 363 patients (CSU: 267; SjS: 49; asthma: 47) who received various doses (10-100 mg QD/BID) of remibrutinib for 12-52 weeks were included
- Across the CSU, SjS, and asthma studies, the most frequently reported grouped AEs (≥10%) were Infections and infestations, Skin and subcutaneous tissue disorders, Gastrointestinal diseases, and Nervous system disorders

REMIBRUTINIB IN CSU

- The proportions of patients with ≥1 AE, patients with an AE leading to treatment discontinuation, and patients with SAEs on remibrutinib treatment were similar in the core and extension studies (**Table 1**)
  - No deaths occurred during the core and extension studies
  - The analyses of laboratory parameters, vital signs, and ECG findings did not reveal any significant safety concerns
- Overall, remibrutinib up to 100 mg BID was well tolerated during long-term treatment, with mostly nonserious AEs that were mild to moderate in nature (**Table 1**)
- The incidence of these AEs remained stable during long-term treatment with remibrutinib, with the exception of skin disorders, where an imbalance was observed due to CSU flares after the last dose of study treatment (**Table 1**)
- The incidence of AESIs, including minor hemorrhages and cytopenia, remained stable with long-term treatment (**Table 1**)

Table 1. Remibrutinib in CSU: Overall Safety Profile

	Core study (12 weeks)		Extension study (52 weeks)
Patients, n (%)	**Remibrutinib, any dose (n=267)**	**Placebo (n=42)**	**Remibrutinib 100 mg BID (N=183*)**
Duration of exposure, weeks, median (IQR)	12 (12.0-12.3)	12 (12.1-12.7)	35 (14.4-52.0)
Patients with ≥1 AE	155 (58.1)	18 (42.9)	105 (57.4)
Discontinued study treatment due to AE(s)	7 (2.6)	0	6 (3.3)
Patients with SAE(s)	5 (1.9)	0	4 (2.2)
Deaths	0	0	0
Most frequently reported grouped AEs† (≥10%)			
Infections and infestations (*mostly upper respiratory tract infections*)	64 (24.0)	9 (21.4)	42 (23.0)
Skin and subcutaneous tissue disorders	45 (16.9)	2 (4.8)	32 (17.5)
Nervous system disorders	35 (13.1)	7 (16.7)	19 (10.4)
Gastrointestinal disorders	30 (11.2)	5 (11.9)	26 (14.2)
AESIs (beyond infections)			
Minor hemorrhages	18 (6.7)	1 (2.4)	8 (4.4)
Cytopenia	8 (3.0)	1 (2.4)	1 (0.5)

AE, adverse event; AESI, adverse event of special interest; BID, twice daily; CSU, chronic spontaneous urticaria; IQR, interquartile range; MedDRA, Medical Dictionary for Regulatory Activities; n, number of patients included in each group; N, total number of patients; SAE, serious adverse event
*At the time of the interim analysis (July 2021); †Events are grouped by body system, as per MedDRA (version 24.0) System Organ Class Preferred Term

REMIBRUTINIB IN SjS

- In patients with SjS, the incidence of AEs was generally similar across treatment groups (**Table 2**)
- Remibrutinib had a favorable safety profile and was well tolerated over 24 weeks in patients with SjS (**Table 2**)

Table 2. Remibrutinib in SjS: Overall Safety Profile

Patients, n (%)	**Remibrutinib, any dose (n=49)**	**Placebo (n=24)**	**Total (N=73)**
Patients with ≥1 AE	43 (87.8)	20 (83.3)	63 (86.3)
Discontinued study treatment due to AE(s)	7 (14.3)	2 (8.3)	9 (12.3)
Patients with SAE(s)	2 (4.1)	1 (4.2)	3 (4.1)
Most frequently reported grouped AEs* (≥10%)			
Infections and infestations	20 (40.8)	10 (41.7)	30 (41.1)
Skin and subcutaneous tissue disorders	12 (24.5)	4 (16.7)	16 (21.9)
Nervous system disorders	10 (20.4)	8 (33.3)	18 (24.7)
Gastrointestinal disorders	16 (32.7)	7 (29.2)	23 (31.5)
AESIs (beyond infections)			
Minor hemorrhages	5 (10.2)	2 (8.3)	7 (9.6)
Cytopenia	6 (12.2)	5 (20.8)	11 (15.1)

AE, adverse event; AESI, adverse event of special interest; MedDRA, Medical Dictionary for Regulatory Activities; n, number of patients included in each group; N, total number of patients; SAE, serious adverse event; SjS, Sjögren's syndrome
*Events are grouped by body system, as per the MedDRA (version 24.0) System Organ Class Preferred Term

REMIBRUTINIB IN ASTHMA

- In patients with asthma, the rate of AEs was similar between the remibrutinib and placebo groups (**Table 3**)
  - All AEs were mild or moderate and no participants reported any SAEs
  - No deaths occurred in the study
- There were no clinically meaningful differences in laboratory, ECG, or vital sign findings between the remibrutinib and placebo groups
- Remibrutinib 100 mg QD was safe and well tolerated in patients with asthma (**Table 3**)

Table 3. Remibrutinib in Asthma: Overall Safety Profile

Patients, n (%)	**Remibrutinib 100 mg QD (n=47)**	**Placebo QD (n=29)**	**Total (N=76)**
Patients with ≥1 AE	24 (51.1)	15 (51.7)	39 (51.3)
Discontinued study treatment due to AE(s)	0	2 (6.9)	2 (2.6)
Patients with SAE(s)	0	0	0
Most frequently reported grouped AEs*			
Infections and infestations	11 (23.4)	13 (44.8)	24 (31.6)
Skin and subcutaneous tissue disorders	2 (4.3)	1 (3.4)	3 (3.9)
Nervous system disorders	2 (4.3)	0	2 (2.6)
Gastrointestinal disorders	3 (6.4)	1 (3.4)	4 (5.3)
AESIs (beyond infections)			
Hemorrhages	0	0	0
Cytopenia	0	0	0

AE, adverse event; AESI, adverse event of special interest; MedDRA, Medical Dictionary for Regulatory Activities; n, number of patients included in each group; N, total number of patients; QD, once daily; SAE, serious adverse event
*Events are grouped by body system, as per the MedDRA (version 24.0) System Organ Class Preferred Term

REFERENCES: 1. Wiendl H et al. Poster presented at: *AAN 2022*; P7-003. **2.** Pulz R et al. Poster presented at: *ECTRIMS 2022*; EPO0896.

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