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Safety of Remibrutinib Across Immune-Mediated Diseases Supports Development in Multiple Sclerosis

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KEY FINDINGS & CONCLUSIONS

- Integrated safety analysis of remibrutinib based on pooled data from phase 2 studies in different immune-mediated conditions confirmed that remibrutinib has a favorable safety profile and is well tolerated across indications and doses, including 100 mg bid with treatment up to 52 weeks
- Remibrutinib's consistently favorable safety profile supports its ongoing development in phase 3 clinical trials in multiple sclerosis

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INTRODUCTION

- Remibrutinib is a novel, potent, highly selective, covalent, oral Bruton's tyrosine kinase inhibitor[1,2]
- The ongoing remibrutinib clinical development program comprises >20 studies, with >1700 patients exposed to remibrutinib at doses of up to 600 mg/day and durations of up to 52 weeks
- Remibrutinib's improved target selectivity has the potential to result in a favorable safety profile by minimizing off-target effects[1,2]
- Remibrutinib is currently being evaluated in 2 pivotal phase 3 trials in multiple sclerosis (MS) (REMODEL-1 [NCT05147220] and REMODEL-2 [NCT05156281]) designed to establish the therapeutic potential of remibrutinib as novel treatment in relapsing MS[3]

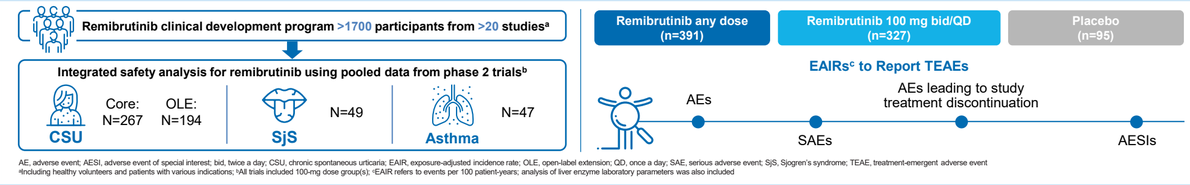
OBJECTIVE

- To report the integrated safety profile of remibrutinib across different immune-mediated conditions using pooled data from completed phase 2 clinical trials, including long-term remibrutinib treatment of up to 52 weeks

METHODS

- Pooled data from completed phase 2 studies of chronic spontaneous urticaria (CSU, [NCT0392661]; including the 52-week open-label extension [NCT04109313]), Sjögren syndrome (SjS, [NCT04035668]), and asthma (NCT03944707) were analyzed (**Figure 1**)

Figure 1. Study Population and Assessments



AE, adverse event; AESI, adverse event of special interest; bid, twice a day; CSU, chronic spontaneous urticaria; EAIR, exposure-adjusted incidence rate; OLE, open-label extension; QD, once a day; SAE, serious adverse event; SjS, Sjogren's syndrome; TEAE, treatment-emergent adverse event
[a]Including healthy volunteers and patients with various indications; [b]All trials included 100-mg dose group(s); [c]EAIR refers to events per 100 patient-years; analysis of liver enzyme laboratory parameters was also included

RESULTS

Patient Demographics

- Mean age at baseline for patients across the different analysis groups was 46.5-48.9 years
- The majority of patients were White (>75%) and women (>70%)

Overall Safety Profile of Remibrutinib

- The rates of overall adverse events (AEs) were generally comparable among the remibrutinib any dose group, the remibrutinib 100 mg dose group, and the placebo group (**Table 1**)
- Remibrutinib was well tolerated: AEs leading to treatment discontinuation, serious AEs, and severe AEs were infrequent and without dose dependency

Table 1. Overall Safety Profile (EAIR[a], 95% [CI])

	Remibrutinib any dose (n=391)	Remibrutinib 100 mg bid/QD (n=327)	Placebo (n=95)
Any AE	260.8 (231.5-292.8)	224.8 (197.0-255.4)	350.3 (262.4-458.1)
AEs leading to treatment discontinuation	8.3 (5.3-12.3)	8.3 (5.1-12.8)	13.6 (3.7-34.8)
Any SAE	4.2 (2.2-7.3)	2.9 (1.2-6.0)	3.4 (0.1-18.7)
Severe AEs	5.2 (2.9-8.6)	4.6 (2.3-8.2)	0.0 (0.0-12.3)

AE, adverse event; bid, twice a day; EAIR, exposure-adjusted incidence rate; QD, once a day; SAE, serious adverse event
[a]EAIR refers to events per 100 patient-years

AESIs

- The most frequently reported grouped adverse events of special interest (AESIs) were infections: most were mild to moderate in severity and the majority were upper respiratory tract infections and nasopharyngitis (**Table 2**)
- Bleeding events were all mild to moderate and mostly cutaneous
- Cytopenias were rare and all mild to moderate
- Overall, rates of AESIs were similar across remibrutinib groups and with placebo

Table 2. AESIs (EAIR[a], 95% [CI])

	Remibrutinib any dose (n=391)	Remibrutinib 100 mg bid/QD (n=327)	Placebo (n=95)
Infections (most mild to moderate)	**68.0 (57.3-80.0)**	**58.5 (48.1-70.5)**	**136.4 (92.7-193.7)**
Nasopharyngitis	13.2 (9.2-18.2)	8.5 (5.2-13.2)	43.8 (22.7-76.6)
URTI	6.4 (3.8-10.1)	5.5 (2.9-9.3)	24.5 (9.9-50.5)
Bleeding (all mild to moderate)	**12.5 (8.7-17.5)**	**11.3 (7.4-16.5)**	**10.3 (2.1-30.2)**
Petechiae	2.4 (1.0-5.0)	2.5 (0.9-5.4)	0.0 (0.0-12.3)
Hematuria[b]	1.0 (0.2-3.0)	0.8 (0.1-3.0)	0.0 (0.0-12.3)
Gingival bleeding	0.7 (0.1-2.5)	0.4 (0.0-2.3)	0.0 (0.0-12.3)
Cytopenia (all mild to moderate)	**5.7 (3.2-9.2)**	**5.1 (2.6-8.9)**	**21.3 (7.8-46.4)**
Neutropenia	2.4 (1.0-5.0)	2.1 (0.7-4.9)	6.8 (0.8-24.5)

AESI, adverse event of special interest; bid, twice a day; EAIR, exposure-adjusted incidence rate; QD, once a day; URTI, upper respiratory tract infection
[a]EAIR refers to events per 100 patient-years; [b]Hematuria was lab detected and does not refer to clinical hematuria

Most Frequently Reported Grouped AEs[a]

- The rates of most frequently grouped AEs were generally comparable between the remibrutinib groups, as well as with placebo (**Table 3**)

Liver Enzyme Abnormalities

- Across the completed phase 2 trials of remibrutinib, newly occurring notable liver enzyme elevations were single instances only and were all asymptomatic and transient/reversible:
  - **CSU core study:** single case of transient, asymptomatic alanine aminotransferase (ALT) elevation of 7× the upper limit of normal (ULN; without elevation in bilirubin level); resolved while on treatment[4]
  - **CSU open-label extension study:** 2 newly occurring liver enzyme increases, 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[5]
  - **Asthma study:** single case of transient, asymptomatic aspartate transaminase elevation of 3× ULN (without elevation in bilirubin level); resolved while on treatment
  - **SjS study:** no cases

Table 3. Most Frequently Reported Grouped AEs (EAIR[a], ≥20, 95% [CI])

	Remibrutinib any dose (n=391)	Remibrutinib 100 mg bid/QD (n=327)	Placebo (n=95)
GI disorders	**31.7 (25.1-39.6)**	**28.8 (22.0-37.0)**	**48.6 (25.9-83.2)**
Nausea	6.8 (4.1-10.6)	5.5 (2.9-9.5)	6.9 (0.8-25.0)
Diarrhea	6.8 (4.1-10.6)	5.5 (2.9-9.4)	10.4 (2.1-30.4)
Skin disorders	**40.1 (32.5-49.0)**	**35.0 (27.4-44.0)**	**25.3 (10.2-52.1)**
Petechiae	2.4 (1.0-5.0)	2.5 (0.9-5.4)	0.0 (0.0-12.3)
CSU	12.1 (8.4-16.9)	11.0 (7.2-16.1)	3.4 (0.1-18.7)
Nervous system	**25.5 (19.6-32.5)**	**20.5 (15.0-27.4)**	**60.4 (33.8-99.6)**
Headache	15.8 (11.4-21.4)	11.4 (7.4-16.6)	41.3 (20.6-73.8)
Musculoskeletal	**21.6 (16.3-28.1)**	**21.2 (15.5-28.2)**	**25.3 (10.2-52.2)**
Arthralgia	3.9 (1.9-6.9)	3.8 (1.7-7.2)	6.8 (0.8-24.6)

AE, adverse event; bid, twice a day; CSU, chronic spontaneous urticaria; EAIR, exposure-adjusted incidence rate; QD, once a day; URTI, upper respiratory tract infection
[a]Infections were the most frequent grouped AEs and are described in the Table 2; [b]EAIR refers to events per 100 patient-years

Disclosures

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