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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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CONCLUSIONS

1. **The remibrutinib clinical development program comprises of 17 studies with over 1,000 subjects exposed to remibrutinib at doses ranging from 0.5–600 mg and varying duration of up to 52 weeks**
2. **Safety analysis of Phase 2 studies with remibrutinib in 363 patients with different immune-mediated conditions showed:**
   - **Remibrutinib has a favorable safety and tolerability profile across all dose levels, maintained through treatment up to 52 weeks**
   - **An overall incidence of adverse events comparable between remibrutinib and placebo, with infections (primarily upper respiratory tract infections) as most common AEs**
   - **No significant findings in the analysis of laboratory data for blood cell counts and blood chemistry, including liver enzymes**
3. **Remibrutinib demonstrated a favorable safety profile and was well-tolerated at doses up to 100 mg b.i.d., supporting its development in Phase 3 clinical trials in MS**

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INTRODUCTION

- Remibrutinib is a novel, potent, highly selective, covalent, oral Bruton's tyrosine kinase (BTK) inhibitor currently being investigated in Phase 3 trials for the treatment of multiple sclerosis (MS; NCT05147220/NCT05156281)[1]
- Remibrutinib showed a high selectivity and potency profile in vitro,[2] with the potential to minimize off-target toxicity and associated adverse events (AEs)

Remibrutinib clinical development program

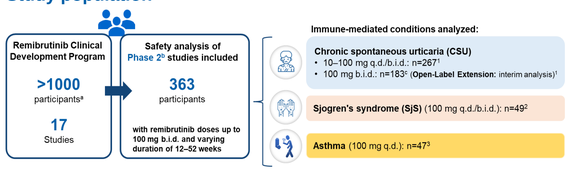
- Across 17 studies, over 1,000 participants (healthy volunteers and patients with various conditions) exposed to remibrutinib at doses ranging from 0.5–600 mg and varying duration of up to 52 weeks
  - Over 250 patients at a dose of 100 mg twice daily (b.i.d.)

OBJECTIVE

To present an overview of the safety of remibrutinib from Phase 2 clinical trials in various immune-mediated conditions

METHODS

Study population



[a]Including healthy volunteers and patients with various indications. [b]Phase 3 program is ongoing and thus, safety analysis is pending. [c]At the time of the interim analysis (July 2021).
b.i.d., twice daily; n, number of patients included in each group; q.d., once daily.

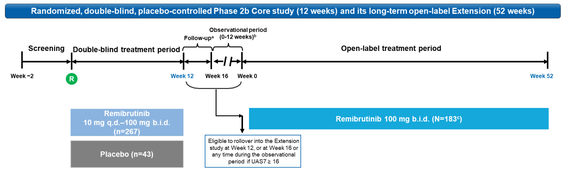
Safety assessments

- AEs
- Serious AEs (SAEs)
- AEs leading to study treatment discontinuation
- AEs of special interest (AESI)
- Vital signs, electrocardiogram (ECG), laboratory parameters

RESULTS

Remibrutinib in CSU[3]

Core and Extension study design



[a]Patients with UAS7<16 at Week 12 were not eligible to rollover into the Extension study but needed to enter the follow-up period of Core study. [b]If UAS7<16 at Week 16, patients 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 entering the open-label treatment period. [c]Data for 183 patients enrolled available at the time of interim analysis (July 2021).
b.i.d., twice daily; CSU, chronic spontaneous urticaria; N, total number of patients; n, number of patients included in each group; q.d., once daily; R, randomisation; UAS7, weekly Urticaria Activity Score

Safety results in CSU

- The proportions of patients with at least one AE, an AE leading to treatment discontinuation, and patients with SAEs on remibrutinib treatment was comparable in the Core and Extension studies (**Table 1**)
  - No deaths occurred during both Core and Extension studies
  - The analysis of laboratory parameters, vital signs, and ECG findings did not reveal any significant safety concerns
- Overall, remibrutinib up to 100 mg b.i.d. was well-tolerated during long-term treatment with mostly non-serious AEs, mild-to-moderate in nature (**Table 1**)

Table 1. Overall safety profile of remibrutinib in patients with CSU

	Core study (12 weeks)		Extension study (52 weeks)
Patients, n (%)	Remibrutinib any dose (n=267)	Placebo (n=42)	Remibrutinib 100 mg b.i.d. (N=183[a])
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 (0.0)	6 (3.3)
Patients with SAE(s)	5 (1.9)	0 (0.0)	4 (2.2)
Death	0 (0.0)	0 (0.0)	0 (0.0)

[a]At the time of the interim analysis (July 2021).
AE, adverse event; b.i.d., twice daily; CSU, chronic spontaneous urticaria; IQR, interquartile range; N, total number of patients; n, number of patients included in each group; SAE, serious adverse event.

- The most frequently reported grouped AEs (≥10%) were infections and infestations, skin and subcutaneous tissue, gastrointestinal, and nervous system disorders (**Table 2**)
  - The incidence of these AEs remained stable during long-term treatment with remibrutinib, with an exception of skin disorders where an imbalance was observed due to CSU flares after the last dose of study treatment
- The incidence of AESI, including hemorrhages and cytopenia, remained stable with long-term treatment

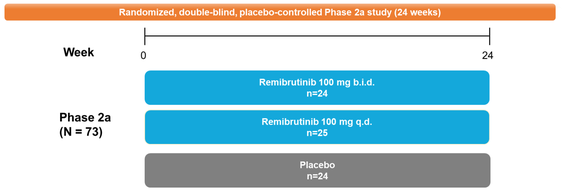
Table 2. Most common grouped AEs and AESI (beyond infection) in CSU

	Core study (12 weeks)		Extension study (52 weeks)
Patients, n (%)	Remibrutinib any dose (n=267)	Placebo (n=42)	Remibrutinib 100 mg b.i.d. (N=183[a])
Most frequently reported grouped AEs[b] (≥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)
AESI (beyond infections)			
Minor hemorrhages	18 (6.7)	1 (2.4)	8 (4.4)
Cytopenia	8 (3.0)	1 (2.4)	1 (0.5)

[a]At the time of the interim analysis (July 2021); [b]Events are grouped by body system, as per the = MedDRA (version 24.0) System Organ Class (SOC) Preferred Term (PT).
AE, adverse event; AESI, AEs of special interest; b.i.d., twice daily; CSU, chronic spontaneous urticaria; MedDRA, Medical Dictionary for Regulatory Activities; N, total number of patients; n, number of patients included in each group

Remibrutinib in SjS[4]

LOUiSSe[a] study design



[a]A study of remibrutinib in SjS.
b.i.d., twice daily; N, total number of patients; n, number of patients included in each group; q.d., once daily; SjS, Sjogren's syndrome

Safety results in SjS

- In patients with SjS, the incidence of AEs was generally comparable across treatment groups (**Table 3**)
- Remibrutinib had a favorable safety profile and was well-tolerated over 24 weeks in patients with SjS

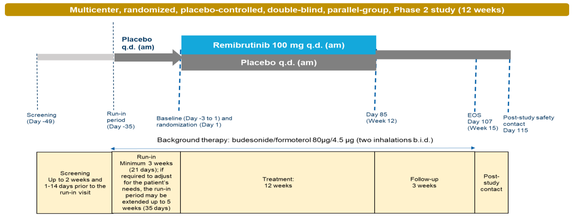
Tables 3. Overall safety profile of remibrutinib in patients with SjS

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[a] (≥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)
AESI (beyond infections)			
Minor hemorrhages	5 (10.2)	2 (8.3)	7 (9.6)
Cytopenia	6 (12.2)	5 (20.8)	11 (15.1)

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

Remibrutinib in asthma[5]

Study design



b.i.d., twice daily; EOS, end of study; q.d., once daily

Safety results in asthma

- In patients with asthma, AE rate was comparable between the remibrutinib and placebo groups (**Table 4**)
  - 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 signs findings between remibrutinib and placebo groups
- Remibrutinib 100 mg q.d. was safe and well-tolerated in patients with asthma

Table 4. Overall safety profile of remibrutinib in patients with asthma

Patients, n (%)	Remibrutinib 100 mg q.d. (n=47)	Placebo q.d. (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 (0.0)	2 (6.9)	2 (2.6)
Patients with SAE(s)	0 (0.0)	0 (0.0)	0 (0.0)
Most frequently reported grouped AEs[a]			
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)
AESI (beyond infections)			
Hemorrhages	0 (0.0)	0 (0.0)	0 (0.0)
Cytopenia	0 (0.0)	0 (0.0)	0 (0.0)

[a]Events are grouped by body system, as per the = MedDRA (version 24.0) System Organ Class (SOC) Preferred Term (PT).
AE, adverse event; AESI, AEs of special interest; MedDRA, Medical Dictionary for Regulatory Activities; N, total number of patients; n, number of patients included in each group; q.d., once daily.

REFERENCES: 1. Wiendl H et al. Poster presented at: American Academy of Neurology; April 2-7, 2022. P7-003 **2.** Puiz R et al. Poster presented at: the 38th congress of the ECTRIMS; October 26-28, 2022. EPO0896 **3.** Giménez-Arnau A et al. Oral session presented at European Academy of Allergy and Clinical Immunology (EAACI), 1-3 July 2022. OAS 3 **4.** Dörner T et al. Plenary presentation at American college of Rheumatology (ACR) convergence, 2022 **5.** Data on file. Clinical Study Report CLOU064D12201. Novartis Pharmaceuticals Corp; Sep 20, 2019.

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