No increased rate of infections and infestations with remibrutinib (LOU064) in Phase 2 studies in patients with chronic spontaneous urticaria

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INTRODUCTION

- Chronic spontaneous urticaria (CSU) is characterised by the spontaneous occurrence of wheals (hives) and/or angioedema for ≥6 weeks and has a major impact on patients' well-being[1]
- Remibrutinib (LOU064), a novel, highly selective and potent covalent oral Bruton's tyrosine kinase inhibitor (BTKi),[2] is currently in Phase 3 development for the treatment of CSU (REMIX-1: NCT05030311, REMIX-2: NCT05032157)[3,4]
- In the Phase 2b study, remibrutinib has demonstrated clinical efficacy and a favourable safety profile versus placebo in patients with CSU[5,6]
- Increased rates of infectious complications are reported in patients with haematologic malignancies treated with approved BTKis[7]

OBJECTIVE

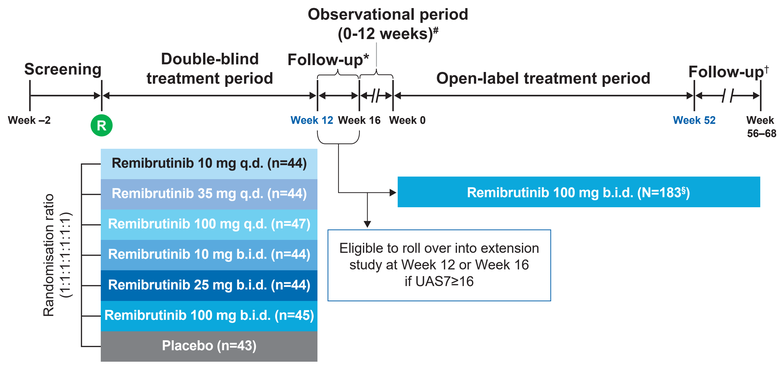
- The present analysis investigates infections and infestations in patients with CSU treated with remibrutinib for up to 52 weeks in the Phase 2 study (NCT03926611) and an interim analysis of data from its extension study (NCT04109313)

METHODS

Study design

- The Phase 2b core study was a double-blind, placebo-controlled, dose-finding study in adult patients with CSU who were randomised (1:1:1:1:1:1:1) to receive remibrutinib 10 mg once daily (q.d.), 35 mg q.d., 100 mg q.d., 10 mg twice daily (b.i.d.), 25 mg b.i.d., 100 mg b.i.d., or placebo for up to 12 weeks (**Figure 1**)
- Eligible patients at the end of the core study were rolled over into an open-label extension study (ongoing) at Week 12 or Week 16 if their weekly Urticaria Activity Score (UAS7) was ≥16, and they received remibrutinib 100 mg b.i.d. for up to 52 weeks (**Figure 1**)

Figure 1. Phase 2b core and its long-term open-label extension study design



*Patients with UAS7<16 at Week 12 are not eligible to roll-over into extension study but need to enter the follow-up period of the core study. #If UAS7<16 at Week 16, patients will be allocated to the observational period of the extension study for up to 12 weeks. After relapse in the extension study (UAS7≥16 at least once), the observational period can be terminated immediately at any time during these 12 weeks and patients may enter the treatment period. †Minimum duration of the follow-up period will be 4 weeks for all patients who stop treatment with remibrutinib. Patients who achieve a UAS7≤6 at Week 52 of the treatment period will extend their follow-up period until they relapse (UAS7≥16). Follow-up will stop at Week 68 for all patients. §Data for 183 patients enrolled available at the time of interim analysis (July 2021).
b.i.d., twice daily; N, total number of patients; n, number of patients included in each group; q.d., once daily; R, randomisation; UAS7, weekly Urticaria Activity Score

Study assessments

- Infectious events reported in the core and extension studies (using broad definition of Medical Dictionary for Regulatory Activities [MedDRA] system organ class [SOC] infections and infestations) were assessed by pathogen type, body system affected, and investigator-reported term (using respective MedDRA structure of high-level group term [HLGT], high-level term [HLT], and preferred term [PT])

RESULTS

- Approximately 90% of patients completed the 12-week treatment in the final analysis of the core study
- At the time of interim analysis of the long-term extension study (median 35.14 weeks, N=183), 36% of patients had completed the full 52-week treatment
- Demographics in the core and extension studies were comparable (**Table 1**)

Table 1. Patient demographics by treatment group

Baseline characteristics	Core study: Remibrutinib 10 mg q.d. (n=44)	35 mg q.d. (n=44)	100 mg q.d. (n=47)	10 mg b.i.d. (n=44)	25 mg b.i.d. (n=44)	100 mg b.i.d. (n=45)	Placebo (n=43)	Total Randomised (N=311)	Extension study: Remibrutinib 100 mg b.i.d. (N=183*)
Age (years)	42.5±16.0	44.0±16.5	45.2±13.4	46.1±15.2	47.4±14.6	44.9±13.8	45.1±15.2	45.0±14.9	45.5±13.5
Gender (female), n (%)	35 (79.5)	30 (68.2)	39 (83.0)	32 (72.7)	32 (72.7)	29 (64.4)	25 (58.1)	222 (71.4)	133 (72.7)
Weight (kg)	78.4±19.4	79.0±20.2	76.7±14.7	78.4±16.8	77.1±19.9	78.9±19.3	78.4±16.5	78.1±18.0	78.0±17.9

Data are expressed as mean±SD unless stated otherwise. *At the time of interim analysis (July 2021).
b.i.d., twice daily; kg, kilogram; N, total number of patients; n, number of patients randomised to each arm; q.d., once daily; SD, standard deviation

- The overall incidence of infections and infestations by SOC for any remibrutinib dose group and the placebo arm in the core study was 24.0% and 21.4%, respectively (**Table 2**), with no apparent dose-dependent pattern; rates were comparable with long-term exposure in the extension study (23.0%; **Table 2**). Most infections by PT, apart from nasopharyngitis, upper respiratory tract infection, COVID-19, and gastroenteritis, were reported in single patients
- Three infectious events were reported as serious due to hospitalisation, all recovered/resolved: renal abscess in a patient treated with remibrutinib 25 mg b.i.d. in the core study and one patient each had appendicitis and COVID-19 in the extension study
- In the core and the extension study, the rate of infections by pathogen type (bacterial, fungal, viral and unspecified pathogen) were comparable between the remibrutinib dose groups and the placebo arm (**Table 2**)

Table 2. Frequency of infections and infestations with remibrutinib from the Phase 2b core and extension studies by pathogen type (safety set)

Patients, n (%)	Core study: Remibrutinib 10 mg q.d. (n=44)	35 mg q.d. (n=44)	100 mg q.d. (n=47)	10 mg b.i.d. (n=44)	25 mg b.i.d. (n=43)	100 mg b.i.d. (n=45)	Any dose (N=267)	Placebo (n=42)	Extension study: Remibrutinib 100 mg b.i.d. (N=183*)
Infections and infestations†	12 (27.3)	9 (20.5)	14 (29.8)	6 (13.6)	12 (27.9)	11 (24.4)	64 (24.0)	9 (21.4)	42 (23.0)
Infections with unspecified pathogen††	11 (25.0)	7 (15.9)	9 (19.1)	5 (11.4)	11 (25.6)	9 (20.0)	52 (19.5)	7 (16.7)	32 (17.5)
Viral infectious disorders††	1 (2.3)	2 (4.5)	4 (8.5)	1 (2.3)	2 (4.7)	2 (4.4)	12 (4.5)	2 (4.8)	10 (5.5)
Bacterial infectious disorders††	1 (2.3)	0 (0.0)	3 (6.4)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.5)	2 (4.8)	6 (3.3)
Fungal infectious disorders††	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.5)

Data are expressed as n (%).
MedDRA version 24.0 has been used for reporting infections and infestations by SOC and HLGT.
Infections with unspecified pathogen = MedDRA HLGT infections - pathogen unspecified.
*At the time of interim analysis (July 2021); †defined by SOC; ††defined by HLGT.
b.i.d., twice daily; HLGT, high-level group term; MedDRA, Medical Dictionary for Regulatory Activities; N, total number of patients;
n, number of patients randomised to each arm; q.d., once daily; SOC, system organ class

- Among infections with unspecified pathogen, upper respiratory tract infections were the most common adverse events (AEs), with rates comparable between any remibrutinib dose group and the placebo arm in the core study (13.1% and 14.3%), and not increasing with longer remibrutinib exposure (8.2% in the extension study; **Table 3**)
  - Nasopharyngitis was the most common upper respiratory tract infection, with 8.6% in any remibrutinib dose group, 7.1% in the placebo arm in the core study and 3.3% in the extension study
  - The remaining most common AEs with unspecified pathogens were urinary tract infections (any remibrutinib dose group and placebo arm in core study: 3.4% and 0%; 3.3% in the extension study); followed by abdominal and gastrointestinal infections (any remibrutinib dose group and placebo arm in core study: 1.9% and 2.4%; 4.4% in the extension study)
- Among viral infectious disorders, coronavirus infections were the most common, reflecting the impact of the pandemic: 1.1% in any remibrutinib dose group, 2.4% in the placebo arm in the core study, and 5.5% in the extension study (with patients enrolled and treated almost entirely during the pandemic phase; **Table 3**)
  - All COVID-19 infections were mild or moderate and recovered/resolved in the core study; one patient in the extension study was hospitalised due to serious COVID-19 infection
- Unspecified bacterial infections were the most common among reported bacterial infections in 1.5% and 4.8% of patients in the any remibrutinib dose group and the placebo arm in the core study, respectively, and 2.2% in the extension study (**Table 3**)
- Unspecified fungal infections were the most common among reported fungal infections and were rare – 0.4% and 0% of patients in any remibrutinib dose group and the placebo arm in the core study, respectively, and 0.5% in the extension study (**Table 2**)

Table 3. Frequency of infections and infestations with remibrutinib from the Phase 2b core and extension studies by pathogen type and investigator-reported term (safety set)

Patients, n (%)	Core study: Remibrutinib 10 mg q.d. (n=44)	35 mg q.d. (n=44)	100 mg q.d. (n=47)	10 mg b.i.d. (n=44)	25 mg b.i.d. (n=43)	100 mg b.i.d. (n=45)	Any dose (N=267)	Placebo (n=42)	Extension study: Remibrutinib 100 mg b.i.d. (N=183*)
Infections with unspecified pathogen (by HGLT)									
Upper respiratory tract infections†	9 (20.5)	6 (13.6)	5 (10.6)	4 (9.1)	7 (16.3)	4 (8.9)	35 (13.1)	6 (14.3)	15 (8.2)
Urinary tract infections†	1 (2.3)	0 (0.0)	3 (6.4)	0 (0.0)	3 (7.0)	2 (4.4)	9 (3.4)	0 (0.0)	6 (3.3)
Abdominal and gastrointestinal infections†	0 (0.0)	1 (2.3)	0 (0.0)	1 (2.3)	1 (2.3)	2 (4.4)	5 (1.9)	1 (2.4)	8 (4.4)
Viral infectious disorders (by HGLT)									
Coronavirus infections†	1 (2.3)	0 (0.0)	1 (2.1)	1 (2.3)	0 (0.0)	0 (0.0)	3 (1.1)	1 (2.4)	10 (5.5)
Influenza viral infections†	0 (0.0)	1 (2.3)	1 (2.1)	0 (0.0)	1 (2.3)	0 (0.0)	3 (1.1)	1 (2.4)	0 (0.0)
Unspecified viral infections†	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	1 (2.3)	2 (4.4)	4 (1.5)	0 (0.0)	0 (0.0)
Bacterial infectious disorders (by HGLT)									
Unspecified bacterial infections†	1 (2.3)	0 (0.0)	3 (6.4)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.5)	2 (4.8)	4 (2.2)

Data are expressed as n (%).
MedDRA version 24.0 has been used for reporting the infections and infestations by SOC, HGLT and HLT.
Infections with unspecified pathogen = MedDRA HLGT infections - pathogen unspecified; Unspecified bacterial infections = MedDRA HLT bacterial infections NEC; Unspecified viral infections = MedDRA HLT viral infections NEC. *At the time of interim analysis (July 2021); †defined by HLT.
b.i.d., twice daily; HLT, high-level term; HLGT, high-level group term; MedDRA, Medical Dictionary for Regulatory Activities; N, total number of patients;
n, number of patients randomised to each arm; NEC, not elsewhere classified; q.d., once daily; SOC, system organ class

CONCLUSIONS

- In this Phase 2b study and its extension, the rate of infections was found to be comparable between remibrutinib and placebo, with rates consistent with long-term exposure up to 52 weeks in the interim analysis of the extension study
- Most infections were of unspecified pathogen, of which upper respiratory tract infection was the most common
- Rates of viral infections were low, with primarily coronavirus ones reported, reflecting the impact of the COVID-19 pandemic. Bacterial and fungal infections were rare
- These data further support the favourable safety profile of remibrutinib in patients with CSU
- Ongoing Phase 3 clinical trials in CSU[3,4] will provide further data on the topic, including long-term exposure up to 52 weeks

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Conflicts of Interest

Martin Metz reports personal fees from Amgen, Aralez, Argenx, AstraZeneca, Celldex, Moxie, Novartis, Roche, Sanofi and Uriach. **Ana Giménez-Arnau** reports roles as a medical advisor for Uriach Pharma, Sanofi and Genentech, Novartis, FAES, GSK, AMGEN, Thermo Fisher and has research grants supported by Uriach Pharma, Novartis and Instituto Carlos III- FEDER, she also participates in educational activities for Uriach Pharma, Novartis, Genentech, Menarini, LEO- PHARMA, GSK, MSD, Almirall, AVENE and Sanofi. **Marcus Maurer** is or recently was a speaker and/or advisor for and/or has received research funding from Amgen, Allakos, Aralez, AstraZeneca, Celldex, FAES, Genentech, GI Innovation, Kyowa Kirin, Leo Pharma, Menarini, Novartis, Moxie, MSD, Roche, Sanofi, Third Harmonic, UCB, and Uriach. **Alberto Tolcachier** reports performing clinical research for Novartis, AstraZeneca, Sanofi Genzyme, GSK and speaker fees from Novartis and Sanofi. **Sibylle Haemmerle**, **Karine Lheritier**, and **Artem Zharkov** are employees of Novartis Pharma AG, Basel, Switzerland.

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