Remibrutinib demonstrates faster time to complete urticaria control in patients with chronic spontaneous urticaria compared with placebo

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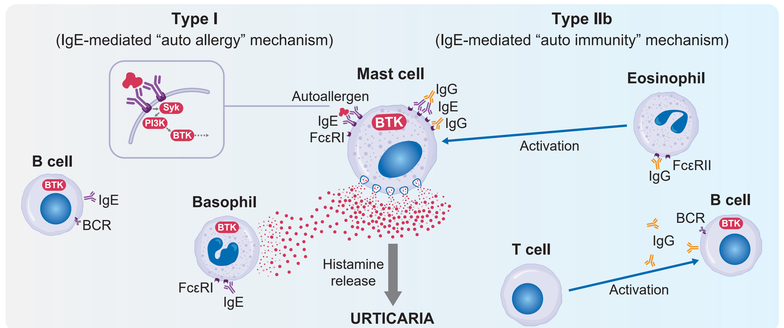
INTRODUCTION

- Chronic spontaneous urticaria (CSU) is characterised by the occurrence of itchy wheals (hives) and/or angioedema for ≥6 weeks and has a substantial impact on patient's quality of life[1,2]
- Skin mast cell activation in CSU occurs via: Type I (autoallergic), driven by immunoglobulin E (IgE) to autoallergens, and Type IIb (autoimmune) due to mast cell-targeted autoantibodies against IgE or FcεRI[3] (**Figure 1**)
- Bruton's tyrosine kinase inhibitors (BTKis) have potential efficacy in both Type I and Type IIb CSU due to inhibition of autoantibody production in B cells and BTK-mediated degranulation in mast cells[1]

Figure 1. BTK inhibition in immune-mediated dermatological conditions



BCR, B cell receptor; BTK, Bruton's tyrosine kinase; FcεRI/II, high-affinity IgE receptor I/II; Ig, immunoglobulin; PI3K, phosphoinositide 3-kinase; SyK, spleen tyrosine kinase

- Despite several treatment options, up to 55% of patients with CSU respond inadequately to second-generation H_1-antihistamines[4]
- There is a considerable unmet need for effective, safe oral therapies for CSU with a novel mechanism of action[5,6]
- Remibrutinib (LOU064), a highly selective and potent covalent novel oral BTKi, has demonstrated clinical efficacy and a favourable safety profile in a Phase 2b dose-finding study (NCT03926611) for patients with moderate to severe CSU[7]

OBJECTIVE

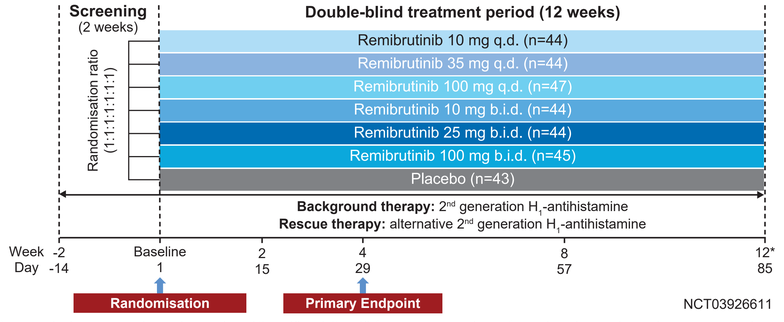
- The current analysis aimed to report time to first weekly Urticaria Activity Score (UAS7) responses in patients with moderate to severe CSU from the Phase 2b study

METHODS

Study design

- This was a dose-finding, multicentre, randomised, double-blind, placebo-controlled Phase 2b study conducted at 82 sites in 17 countries in patients with CSU (**Figure 2**)

Figure 2. Study design



*Eligible patients rolled over into an extension study at Week 12 or at Week 16, following roll-over criteria defined in the extension study protocol and dependent on HAs/EC approval from participating countries. Background therapy was a second-generation H_1-antihistamine at a locally approved licensed posology that had to be administered daily with a stable treatment regimen throughout the study. Rescue therapy was a second-generation H_1-antihistamine at a locally approved licensed posology that differed from the background H_1-antihistamine, is eliminated primarily via renal excretion, and could only be given to treat unbearable symptoms (itch) of CSU on a day-to-day basis.
b.i.d., twice daily; CSU, chronic spontaneous urticaria; EC, ethics committee; HAs, health authorities; n, number of patients randomised in each group; q.d, once daily

Study outcomes

- Outcomes included time to first UAS7=0 (complete absence of hives and itch), time to first UAS7≤6 (well-controlled disease), and response rate for achieving UAS7=0 and UAS7≤6 over time up to Week 12

RESULTS

- Baseline demographics and disease characteristics were generally balanced between treatment arms (**Table 1**)[8]

Table 1. Baseline demographics and disease characteristics (randomised set)[8]

Baseline characteristics	Remibrutinib 10 mg q.d. (n=44)	Remibrutinib 35 mg q.d. (n=44)	Remibrutinib 100 mg q.d. (n=47)	Remibrutinib 10 mg b.i.d. (n=44)	Remibrutinib 25 mg b.i.d. (n=44)	Remibrutinib 100 mg b.i.d. (n=45)	Placebo (n=43)	Total (N=311)
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
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)
DLQI score	14.9±7.1	12.6±6.5	12.7±7.1	12.7±6.2	12.9±6.6	10.8±6.7	13.4±7.9	12.8±6.9
UAS7 score	31.4±7.1	31.2±7.2	28.5±7.0	29.8±6.7	29.3±7.9	29.3±6.0	27.6±7.6	29.6±7.1
Duration of CSU (years)	6.2±7.7	5.9±8.8	5.3±5.8	4.9±5.5	3.8±4.5	4.5±5.2	3.6±4.8	4.9±6.2
Baseline AAS7>0, n (%)	28 (63.6)	23 (52.3)	24 (51.1)	20 (45.5)	22 (50.0)	24 (53.3)	20 (46.5)	161 (51.8)
Previous experience of angioedema, n (%)	26 (59.1)	29 (65.9)	27 (57.4)	28 (63.6)	22 (50.0)	23 (51.1)	22 (51.2)	177 (56.9)

Data are presented as mean±SD, unless stated otherwise.
AAS7, weekly Angioedema Activity Score; b.i.d., twice daily; CSU, chronic spontaneous urticaria; DLQI, Dermatology Life Quality Index; N, total number of patients; n, number of patients randomised to each arm; q.d., once daily; SD, standard deviation; UAS7, weekly Urticaria Activity Score

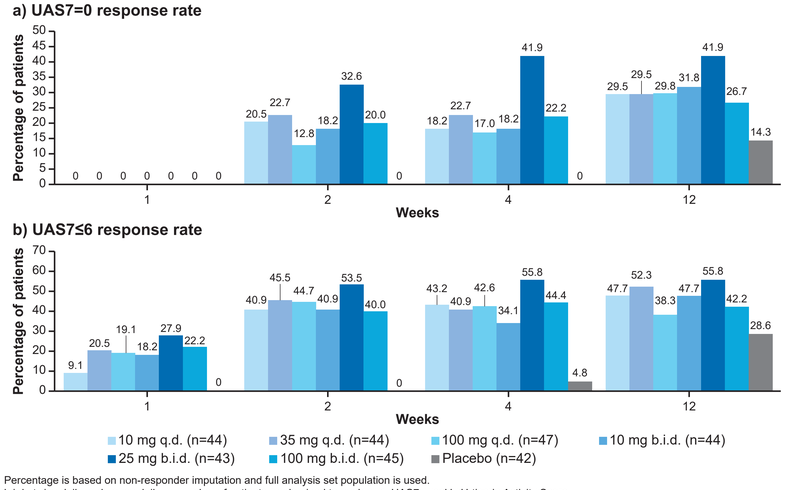
- The median time to first UAS7=0 and UAS7≤6 was shortest with remibrutinib 25 mg b.i.d. (4 and 2 weeks, respectively), compared to other remibrutinib arms, and was not estimable for placebo (**Table 2**)
- Complete response (UAS7=0) and well-controlled disease (UAS7≤6) were achieved faster as early as Week 2 and Week 1, respectively, and in a greater proportion of patients on remibrutinib versus placebo during the study (**Figure 3a–b**)

Table 2. Median time to first UAS7=0 and UAS7≤6 during 12-week Phase 2b study

	Median time to first UAS7=0 and UAS7≤6						
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)**	**Placebo (n=42)**
UAS7=0	NE	12	NE	NE	4	11	NE
UAS7≤6	3	3	3	4.5	2	3	NE

b.i.d., twice daily; q.d., once daily; n, number of patients randomised to each arm; NE, not estimable; UAS7, weekly Urticaria Activity Score

Figure 3. Percentage of patients with a) UAS7=0 response rate and b) UAS7≤6 response rate during the study



Percentage is based on non-responder imputation and full analysis set population is used.
b.i.d., twice daily; q.d., once daily; n, number of patients randomised to each arm; UAS7, weekly Urticaria Activity Score

- Remibrutinib was generally well tolerated across the entire dose range; most adverse events were mild or moderate, with no apparent dose-dependent pattern in terms of type and severity of events (**Table 3**)
- Laboratory parameters did not reveal significant safety concerns and no clinically meaningful changes in vital signs were observed

Table 3. Safety profile of remibrutinib

Patients, n (%)	Remibrutinib 10 mg q.d. (n=44)	Remibrutinib 35 mg q.d. (n=44)	Remibrutinib 100 mg q.d. (n=47)	Remibrutinib 10 mg b.i.d. (n=44)	Remibrutinib 25 mg b.i.d. (n=43)	Remibrutinib 100 mg b.i.d. (n=45)	Remibrutinib Any dose (N=267)	Placebo (n=42)
Most frequent AEs by primary system organ class (≥10% of all patients receiving any remibrutinib dose)								
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)
Skin and subcutaneous tissue disorders*	7 (15.9)	9 (20.5)	5 (10.6)	6 (13.6)	12 (27.9)	6 (13.3)	45 (16.9)	2 (4.8)
Nervous system disorders	3 (6.8)	10 (22.7)	7 (14.9)	4 (9.1)	6 (14.0)	5 (11.1)	35 (13.1)	7 (16.7)
Gastrointestinal diseases	7 (15.9)	4 (9.1)	6 (12.8)	6 (13.6)	2 (4.7)	5 (11.1)	30 (11.2)	5 (11.9)
Most frequent AEs by PT (≥10% of patients in any treatment group)								
Headache	1 (2.3)	7 (15.9)	4 (8.5)	3 (6.8)	6 (14.0)	5 (11.1)	26 (9.7)	6 (14.3)
Nasopharyngitis	7 (15.9)	2 (4.5)	2 (4.3)	4 (9.1)	4 (9.3)	4 (8.9)	23 (8.6)	3 (7.1)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Patients with SAE(s)†	1 (2.3)	0 (0.0)	0 (0.0)	2 (4.5)	2 (4.7)	0 (0.0)	5 (1.9)	0 (0.0)

MedDRA version 24.0 was used for reporting.
*The difference in skin and subcutaneous tissue disorders is primarily driven by CSU flare-ups; most of these events were reported in the treatment-free follow-up period and were mostly mild.
†SAEs: renal abscess (25 mg b.i.d., treatment discontinuation); worsening of lymphadenopathy (10 mg q.d.; present before study start); ureterolithiasis (10 mg b.i.d.; during treatment-free follow-up period); flare/aggravation of CSU (10 mg b.i.d. and 25 mg b.i.d.).
AE, adverse event; b.i.d., twice daily; MedDRA, Medical Dictionary for Regulatory Activities; N, total number of patients; n, number of patients randomised in each arm; PT, preferred term; q.d., once daily; SAE, serious AE

CONCLUSIONS

- In the Phase 2b dose-finding study, patients treated with remibrutinib showed a well-controlled disease status as early as Week 1
  - The median time to first UAS7=0 and UAS7≤6 was shortest with remibrutinib 25 mg b.i.d.
- Complete response and well-controlled disease were reached faster and achieved by a higher percentage of patients with remibrutinib compared with placebo
  - Percentage of patients achieving UAS7=0 and UAS7≤6 responses were higher at Week 2, Week 4, and Week 12 in remibrutinib arms compared with placebo arm
  - As early as Week 2, up to 32.6% of patients (in the 25 mg b.i.d. arm) reached complete response versus 0% in the placebo arm
- Remibrutinib showed a favourable safety profile across all doses
- Findings from the present analysis will be further confirmed in the ongoing Phase 3 clinical trials in CSU[9,10]

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Conflicts of Interest

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, GInnovation, Kyowa Kirin, Leo Pharma, Menarini, Novartis, Moxie, MSD, Roche, Sanofi, Third Harmonic, UCB, and Uriach. **Paul Yamauchi** reports roles as an investigator, consultant, and speaker for Abbvie, Amgen, Novartis, Lilly, Sun Pharma, Janssen, Pfizer, Regeneron, Sanofi, Leo, Incyte. Investigator and consultant for Arcutis, Dermavant, Boehringer Ingelheim. Investigator for Astra Zeneca, Consultant for Evelo Biosciences. **Holly Kanavy** has nothing to declare. **Ana Giménez-Arnau** reports roles as a Medical Advisor for Uriach Pharma, Sanofi Genentech, Novartis, FAES, GSK, Amgen, and 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. **John Reed** reports roles as a medical advisor and has participated in educational activities for Novartis. **Petra Staubach** has received research funding and/or fees for consulting and/or lectures from Novartis, CSL Behring, Shire, MSD, Schering-Plough, Abbvie, Viropharma, Leo Pharma, Pohl-Boskamp GmbH, Astella, Allergika, Karrer, Allmirall, Sanofi, Octapharma, Pfleger GmbH, Beiersdorf, L'Oreal, Lily, Janssen, Celgene, Hermal, UCB, Allmirall, Astelas, Sobi, and Pfizer. **Mark Lebwohl** is an employee of Mount Sinai and receives research funds from AbbVie, Amgen, Arcutis, Avotres, Boehringer Ingelheim, Dermavant Sciences, Eli Lilly, Incyte, Janssen Research & Development, LLC, Ortho Dermatologics, Regeneron, and UCB, Inc., and is a consultant for Aditum Bio, Almirall, AltruBio Inc., AnaptysBio, Arcutis, Aristea Therapeutics, Arrive Technologies, Avotres Therapeutics, BiomX, Boehringer Ingelheim, Bristol-Myers Squibb, Cara Therapeutics, Castle Biosciences, Corrona, Dermavant Sciences, Dr. Reddy's Laboratories, Evelo Biosciences, Evommune, Inc., facilitation of International Dermatology Education, Forte Biosciences, Foundation for Research and Education in Dermatology, Helsinn Therapeutics, Hexima Ltd., LEO Pharma, Meiji Seika Pharma, Mindera, Pfizer, Seanergy, and Verrica. **Ivan Nikolaev**, **Karine Lheritier**, and **Sibylle Haemmerle** are employees of Novartis Pharma AG, Basel, Switzerland. **Pauline Walsh** is an employee of Novartis Ireland Limited, Dublin, Ireland.

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