Efficacy, safety, and tolerability of remibrutinib (LOU064) in CSU patients: Study design of Phase 3b extension trial

TP-C171

Marcus Maurer,[1,2] Ana M Giménez-Arnau,[3] Sarbjit Saini,[4] Mark Lebwohl,[5] Gordon Sussman,[6] Michihiro Hide,[7,8] Karine Lheritier,[9] Artem Zharkov,[9] Simi Bhat,[10] Luna Wei,[11] El-Djouher Martzloff,[9] Sibylle Haemmerle,[9]

[1]Urticaria Center of Reference and Excellence (UCARE), Institute of Allergology, Charité–Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt–Universität zu Berlin, Berlin, Germany; [2]Fraunhofer Institute for Translational Medicine and Pharmacology (ITMP), Allergology and Immunology, Berlin, Germany; [3]Department of Dermatology, Hospital del Mar–IMIM, Universitat Pompeu Fabra, Barcelona, Spain; [4]Division of Allergy and Clinical Immunology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; [5]Department of Dermatology, Icahn School of Medicine at Mt. Sinai, New York, USA; [6]Division of Allergy and Clinical Immunology, University of Toronto, Toronto, Canada; [7]Department of Dermatology, Hiroshima University, Hiroshima, Japan; [8]Department of Dermatology, Hiroshima Citizens Hospital, Hiroshima, Japan; [9]Novartis Pharma AG, Basel, Switzerland; [10]Novartis Healthcare Pvt. Ltd. Hyderabad, India; [11]China Novartis Institutes for Biomedical Research Co. Ltd.

Introduction

- Chronic spontaneous urticaria (CSU) is defined as the spontaneous occurrence of itchy wheals (hives), angio-oedema or both, for more than 6 weeks[1]
- Bruton's tyrosine kinase (BTK) inhibition, a promising therapeutic approach, impairs signalling downstream of FcεRI, which induces mast cell activation[2] and is being explored for the treatment of CSU[3]
- Remibrutinib (LOU064) is an oral, highly selective BTK inhibitor[3] that offers fast disease control in patients with CSU who remain symptomatic despite treatment with second-generation H_1-antihistamines and is currently in Phase 3 development for the treatment of CSU (REMIX-1: NCT05030311, REMIX-2: NCT05032157, BISCUIT: NCT05048342)[4-6]
- Remibrutinib has shown clinical efficacy and a favourable safety profile for up to 12 weeks in the Phase 2b dose-finding study (NCT03926611) and for up to 52 weeks in its open label extension study (NCT04109313) in patients with moderate to severe CSU inadequately controlled by H_1-antihistamines[7,8]

Objective

- To present the study design of remibrutinib Phase 3b extension trial for CSU patients inadequately controlled by second-generation H_1-antihistamines and who completed the preceding remibrutinib Phase 3 studies

Methods

Study Design

- This Phase 3b (NCT05513001), multicentre, double-blind, placebo-controlled, randomised withdrawal and open-label extension study is evaluating the long-term efficacy, safety and tolerability of remibrutinib in patients with CSU who have completed the treatment phase of remibrutinib in preceding Phase 3 studies (**Figure 1**)
- The study consists of 2 Epochs (Epoch-1 and Epoch-2) with a total study duration of ~160 weeks
  - Epoch-1 is the initial study period for patients who completed the Phase 3 studies and consists of a 24-week randomised withdrawal period with remibrutinib or placebo for patients with a weekly Urticaria Activity Score (UAS7) <16 at the end of the preceding studies OR a 24-week open-label treatment period with remibrutinib for patients with an UAS7 ≥16 at the end of the preceding studies
  - Epoch-2 is the second subsequent study period and consists of 24-week cycles that could either encompass treatment-free observation and/or re-treatment periods with remibrutinib, with or without background H_1-antihistamines
- Patients in the randomised withdrawal period will be stratified based on prior duration of remibrutinib exposure (≤28 weeks and >28 weeks) in the previous Phase 3 studies and geographic region

Patient population

- The study population consists of approximately 1021 (Epoch-1: n = 580; Epoch-2: n = 441) adult patients with CSU who have completed one of the preceding core Phase 3 studies as per protocol
- The key inclusion and exclusion criteria of the patients are listed in **Table 1**

Table 1. Key inclusion and exclusion criteria

Key inclusion criteria
• Male and female adult patients (≥18 years) with CSU • Patients who successfully completed the preceding remibrutinib core studies according to the respective protocols • Written informed consent must be obtained before any assessment is performed • Willing and able to adhere to the study protocol and visit schedule
Key exclusion criteria
• Significant bleeding risk or coagulation disorders • History of GI bleeding • Requirement for anti-platelet and anticoagulant medication • History or current hepatic disease • Evidence of clinically significant CV, neurological, psychiatric, pulmonary, renal, hepatic, endocrine, metabolic, haematological disorders, GI disease, or immunodeficiency that, in the investigator's opinion, would compromise the safety of the patient, interfere with the interpretation of the study results or otherwise preclude participation or protocol adherence of the patient

CSU, chronic spontaneous urticaria; CV, cardiovascular; GI, gastrointestinal.

Study objectives and endpoints

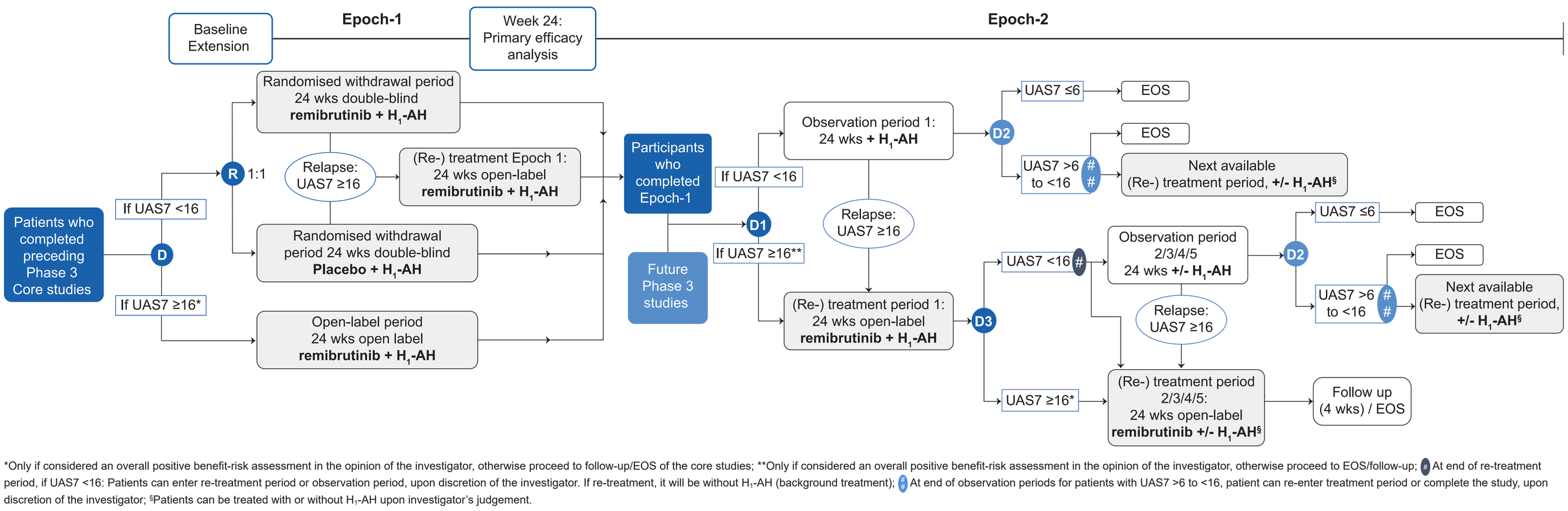
- The primary objective of this study is to assess the efficacy of remibrutinib in patients with CSU with a UAS7 <16 at Week 52 in the prior core study with respect to time to first of the three events: relapse or study treatment discontinuation due to lack of efficacy or intake of strongly confounding prohibited medication up to Week 24 compared to placebo
- The primary and secondary endpoints of the trials are listed in **Table 2**

Table 2. Study endpoints

Primary endpoint
Time to the first composite event of relapse (UAS7 ≥16); or study treatment discontinuation due to lack of efficacy; or first intake of strongly confounding prohibited medication (biologics, cyclosporine or corticosteroids) during the randomised withdrawal period up to Week 24
Secondary endpoint
Safety endpoints will include but not be limited to occurrence of TEAEs (serious and non-serious) during the extension study

TEAEs, treatment-emergent adverse events; UAS7, weekly Urticaria Activity Score.

Figure 1. Study design



*Only if considered an overall positive benefit-risk assessment in the opinion of the investigator, otherwise proceed to follow-up/EOS of the core studies; **Only if considered an overall positive benefit-risk assessment in the opinion of the investigator, otherwise proceed to EOS/follow-up; # At end of re-treatment period, if UAS7 <16: Patients can enter re-treatment period or observation period, upon discretion of the investigator. If re-treatment, it will be without H_1-AH (background treatment); ## At end of observation periods for patients with UAS7 >6 to <16, patient can re-enter treatment period or complete the study, upon discretion of the investigator; §Patients can be treated with or without H_1-AH upon investigator's judgement.

AH, antihistamine; D, decision points; D1, start of Epoch 2; D2, end of each observation period in Epoch 2; D3, end of each treatment period in Epoch 2; EOS, end of study; R, randomisation; UAS7, weekly Urticaria Activity Score; Wks, weeks.

Results

- The enrolment was initiated on 09 December 2022
- A primary efficacy analysis will be conducted on the randomised withdrawal period when all participants have completed their Epoch-1 Week 24 visit or discontinued early. The primary analysis results are expected by Q4 2024

Conclusions

- The results of this Phase 3b study will generate withdrawal data on the rebound effect and the time to relapse, and provide evidence of long-term maintenance of efficacy, safety and tolerability of remibrutinib in CSU

References

1. Zuberbier T, et al. *Allergy*. 2022;77(3):734–766
2. Hata D, et al. *J Exp Med*. 1998; 187:1235–1247
3. Angst D, et al. *J Med Chem*. 2020; 63:5102−5118
4. ClinicalTrial.gov.in. NCT05030311. Accessed on 18th May 2023
5. ClinicalTrial.gov.in. NCT05032157. Accessed on 18th May 2023
6. ClinicalTrial.gov.in. NCT05048342. Accessed on 18th May 2023
7. Maurer M, et al. *J Allergy Clin Immunol*. 2022;150(6):1498–1506.e2
8. Carr W, et al. AAAAI 2023 (Oral Presentation 3611 - Late-breaker)

Disclosures

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; **Ana M Giménez-Arnau** reports roles as a medical advisor for Uriach Pharma, Sanofi and Genentech, Novartis, FAES, GSK, AMGEN, Thermo Fisher, Celldex, Escient 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; **Sarbjit Saini** has received grant/research/clinical trial support from the National Institutes of Health, ITN, Novartis, and Regeneron, and is a consultant/advisory board member for Genentech, Novartis, Medimmune, AstraZeneca, Pfizer, Allakos, Eli Lily, and Gossamer Bio; **Mark Lebwohl** is an employee of Mount Sinai and receives research funds from: Abbvie, Amgen, Arcutis, Avotres, Boehringer Ingelheim, Cara therapeutics, 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, Inc., Aristea Therapeutics, Avotres Therapeutics, Brickell Biotech, Boehringer-Ingelheim, Bristol-Myers Squibb, Cara Therapeutics, Castle Biosciences, Celltrion, Corevitas, Dermavant Sciences, Dr. Reddy, EPI, Evommune, Inc., Facilitatation of \International Dermatology Education, Forte Biosciences, Foundation for Research and Education in Dermatology, Helsinn, Hexima Ltd., Incyte, LEO Pharma, Meiji Seika Pharma, Mindera, Pfizer, Seanergy, Strata, Trevi, and Verrica; **Gordon Sussman** has received research support from Aimmune, Amgen, Astra Zeneca, DBV technologies, Genentech, Kedrion S.p.A, Leo Pharma Inc., Novartis, Nuvo Pharmaceuticals Inc., Sanofi, Stallergenes, Merck, Schering Plough, Regeneron and ALK; is a medical advisor and/or has received payment for lectures from Merck, Novartis, CSL Behring, Pfizer, Anaphylaxis Canada, the Allergy Asthma and Immunology Society of Ontario and the Canadian Hereditary Angioedema Network; **Michihiro Hide** has received lecture and/or consultation fees from Kaken Pharmaceutical, Kyowa Kirin, Mitsubishi Tanabe Pharma, MSD, Novartis, Sanofi, TAIHO Pharmaceutical, Teikoku Seiyaku and Uriach; **Karine Lheritier**, **Artem Zharkov**, **El-Djouher Martzloff** and **Sibylle Haemmerle** are employees of Novartis Pharma AG, Basel, Switzerland; **Simi Bhat** is an employee of Novartis Healthcare Pvt. Ltd. Hyderabad, India; **Luna Wei** is an employee of China Novartis Institutes for Biomedical Research Co. Ltd.

Acknowledgements

All authors participated in the development of the poster for presentation. The authors wish to thank all investigators and patients involved in the trial.
The authors thank Krishna Kammari and Anuja Shah for editorial and medical writing support, and Rupa De for designing support (all Novartis Healthcare Pvt. Ltd., Hyderabad), which was funded by Novartis Pharma AG, Basel, Switzerland, in accordance with the Good Publication Practice (GPP2022) guidelines (https://www.ismpp.org/gpp-2022)

Funding

This investigation was sponsored by Novartis Pharma AG, Basel, Switzerland.
Poster presented at: The European Academy of Allergy and Clinical Immunology (EAACI) Hybrid Congress, Hamburg, Germany, June 9 to 11, 2023.
To download a copy of this poster, visit the web at: https://bit.ly/UKCEAACI

Scan to download a copy of this poster