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Remibrutinib's Safety Across Immune-Mediated Diseases Supports Development in MS

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CONCLUSIONS

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

This study is sponsored by Novartis Pharma AG

Poster Presented at the 31st European Charcot Foundation (ECF) Meeting, 9–11 November 2023, Baveno, Italy

INTRODUCTION

- Remibrutinib is a novel, potent, highly selective, covalent, oral Bruton's tyrosine kinase (BTK) inhibitor[1,2]
- The ongoing remibrutinib clinical development program comprises >20 studies, with >1700 subjects exposed to remibrutinib at doses up to 600 mg/day and duration of up to 52 weeks
- Remibrutinib's improved target selectivity has the potential to result in a favorable safety profile by minimising off-target effects[1,2]
- Remibrutinib is currently being evaluated in two 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 (RMS)[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

STUDY POPULATION & ASSESSMENTS

Remibrutinib clinical development program >1700 participants from >20 studies[a]

Integrated safety analysis for remibrutinib using pooled data from Phase 2 trials[b]

- CSU: Core: N=267, OLE: N=194
- SjS: N=49
- Asthma: N=47

Remibrutinib any dose (n=391)

Remibrutinib 100 mg b.i.d./q.d. (n=327)

Placebo (n=95)

Exposure-adjusted incidence rates (EAIRs)[c] to report treatment-emergent AEs

- Adverse events (AEs)
- Serious AEs (SAEs)
- AEs leading to study treatment discontinuation
- AEs of special interest (AESI)

[a]Including healthy volunteers and patients with various indications. [b]All trials included 100-mg dose group(s); CSU: NCT03926611 (Core), NCT04109313 (OLE); SjS: NCT04035668; asthma: NCT03944707. [c]Exposure-adjusted incidence rate (EAIR) refers to events per 100 patient-years; analysis of liver enzyme laboratory parameters was also included.

b.i.d., twice a day; CSU, chronic spontaneous urticaria; OLE, open-label extension; q.d., once a day; SjS, Sjogren's syndrome.

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 Caucasians (>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 placebo (**Table 1**)
- Remibrutinib was well-tolerated: AEs leading to treatment discontinuation, SAEs 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 b.i.d./q.d. (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)

[a]EAIR refers to events per 100 patient-years.

AE, adverse event; b.i.d., twice a day; CI, confidence interval; EAIR, exposure-adjusted incidence rates; q.d., once a day; SAE, serious AE.

AEs of Special Interest (AESI)

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

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

	Remibrutinib any dose (n=391)	Remibrutinib 100 mg b.i.d./q.d. (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)
Haematuria[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)

[a]EAIR refers to events per 100 patient-years. [b]Haematuria was lab-detected and does not refer to clinical haematuria.

AESI, adverse event of special interest; b.i.d., twice a day; CI, confidence interval; EAIR, Exposure-adjusted incidence rates; URTI, Upper respiratory tract infection; q.d., once a day.

Most Frequently Reported Grouped AEs*

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

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

	Remibrutinib any dose (n=391)	Remibrutinib 100 mg b.i.d./q.d. (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)
Diarrhoea	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)

*Infections were the most frequent grouped AEs and are described in the Table 2. [a]EAIR refers to events per 100 patient-years.

AE, adverse event; b.i.d., twice a day; CI, confidence interval; CSU, chronic spontaneous urticaria; EAIR, exposure-adjusted incidence rates; q.d., once a day; URTI, upper respiratory tract infection.

Liver Enzyme Abnormalities

- Across completed Phase 2 trials of remibrutinib, newly occurring notable liver enzyme elevations were single instances only, all asymptomatic and transient/reversible:
  - **CSU core study:** single case of transient, asymptomatic ALT elevation of 7x ULN (without elevation in bilirubin level); resolved while on treatment[4]
  - **CSU OLE study:** two newly occurring liver enzyme increases, both isolated ALT >3x and <5x 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 AST elevation of 3x ULN (without elevation in bilirubin level); resolved while on treatment
  - **SjS study:** no cases

ALT, alanine transaminase; AST, aspartate transaminase; ULN, upper limit of normal.

Disclosures

Xavier Montalban has received speaking honoraria and travel expenses for participation in scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past years with Abbvie, Actelion, Alexion, Bayer, Biogen, Bristol-Myers Squibb/Celgene, EMD Serono, Genzyme, Hoffmann-La Roche, Immunic, Janssen Pharmaceuticals, Medday, Merck, Mylan, Nervgen, Novartis, Sandoz, Sanofi-Genzyme, Teva Pharmaceutical, TG Therapeutics, Excemed, MSIF and NMSS.**Tanuja Chitnis** has received compensation for consulting from Biogen, Novartis Pharmaceuticals, Roche Genentech and Sanofi Genzyme. She has received research support from the National Institutes of Health, National MS Society, US Department of Defense, Sumaira Foundation, Brainstorm Cell Therapeutics, EMD Serono, I-Mab Biopharma, Mallinckrodt ARD, Novartis Pharmaceuticals, Octave Bioscience, Roche Genentech and Tiziana Life Sciences. Disclosures do not conflict with the work being presented. **Mitzi Williams** has received consulting fees from Alexion, Janssen, TG Therapeutics, Abbvie, Biogen, Bristol Myers Squibb, EMD Serono, Genentech, Inc., Novartis and Sanofi Genzyme along with research support from Biogen Idec, Novartis, Roche Genentech and Sanofi Genzyme. **Laura Airas** has received Institutional research funding from Genzyme and Merck and compensation for lectures and advising from Novartis, Sanofi Genzyme, Merck, Biogen, Roche and Janssen. **Sarbjit Saini** has received grant/research/clinical trial support from the National Institutes of Health, Novartis, Sanofi, Amgen and Regeneron, and is a consultant/advisory board member for Allakos, Granular Therapeutics, Novartis, Aquestive, Regeneron, Escient, Innate, Celltrion and Sanofi. **Michihiro Hide** has received lecture and/or consultation fees from GI Innovation, Kaken Pharmaceutical, Kyowa Kirin, Mitsubishi Tanabe Pharma, MSD, Novartis, Sanofi, TAIHO Pharmaceutical, Teikoku Seiyaku and Uriach. **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. **Jin Nakahara** received speaker honoraria from Abbvie, Alexion, Astellas, Biogen, Chugai, CSL-Behring, Daiichi-Sankyo, Eisai, Fujimoto Pharma, JB, Mitsubishi-Tanabe, Novartis, Otsuka, Sanofi, Sumitomo Dainippon and Takeda. He is acting as a paid consultant for Alexion, Biogen, Chugai, Mitsubishi-Tanabe and Novartis. His research is supported from Abbvie, Biogen, Böehringer-Ingerlheim, Chugai, Daiichi-Sankyo, Eisai, Eli Lilly, JB, Keio University, Kyowa-Kirin, Mitsubishi-Tanabe, MEXT, MHLW, MSD, Otsuka, Pfizer, Shionogi, Sumitomo Dainippon, Takeda and Tsumura. **Robert Bermel** has served as a consultant for Astra Zeneca, Biogen, EMD Serono, Genzyme/Sanofi, Genentech/Roche, Novartis, TG Therapeutics and VielaBio. He receives research support from Biogen, Genentech, and Novartis, and shares rights to intellectual property underlying the Multiple Sclerosis Performance Test, currently licensed to Qr8 Health and Biogen. **Thomas Dörner** has been on advisor or review panel member of AbbVie, Novartis, Bristol-Myers-Squibb, Eli Lilly, UCB, received grant/research support from AbbVie, Novartis, Bristol-Myers-Squibb, Janssen, Roche/Genentech, Eli Lilly, UCBS and has been speaker/Honoraria with Janssen. **Heinz Wiendl** received honoraria for acting as a member of Scientific Advisory Boards for Janssen, Merck and Novartis as well as speaker honoraria and travel support from Alexion, Amicus Therapeuticus, Biogen, Biologix, Bristol Myers Squibb, Cognomed, F. Hoffmann-La Roche Ltd., Gemeinnützige Hertie-Stiftung, Medison, Merck, Novartis, Roche Pharma AG, Genzyme, TEVA and WebMD Global. He is acting as a paid consultant for Biogen, Bristol Myers Squibb, EMD Serono, Idorsia, Immunic, Immunovant, Janssen, Johnson & Johnson, Novartis, Roche, Sanofi, the Swiss Multiple Sclerosis Society and UCB. His research is funded by the German Ministry for Education and Research (BMBF), Deutsche Forschungsgesellschaft (DFG), Deutsche Myasthenie Gesellschaft e.V., Alexion, Amicus Therapeutics Inc., Argenx, Biogen, CSL Behring, F. Hoffmann - La Roche, Genzyme, Merck KgaA, Novartis Pharma, Roche Pharma, UCB Biopharma. **Marcus Maurer** is or recently was a speaker and/or advisor for and/or has received research funding from Allakos, Amgen, Aralez, ArgenX, AstraZeneca, Celldex, Centogene, CSL Behring, FAES, Genentech, GIInnovation, Innate Pharma, Kyowa Kirin, Leo Pharma, Lilly, Menarini, Moxie, Novartis, Roche, Sanofi/Regeneron, Third HarmonicBio, UCB 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. **Brett Loop, Virginia DeLasHeras, Roman Willi, Bernd C. Kieseier, Sibylle Haemmerle, Artem Zharkov, Nathalie Barbier, Amin Azmon, Richard Siegel, Bruno Cenni** are employees of Novartis.

Acknowledgements

Medical writing support was provided by Bhavesh Kshirsagar and Saimithra Thammera and design support by Kuruva Jayaram, employees of Novartis Corporate Center, Hyderabad, India. The final responsibility for the content lies with the authors.

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