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Phase 3 REMODEL I/II Trials: Efficacy, Safety and Tolerability of Remibrutinib in RMS

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CONCLUSIONS

- Remibrutinib is a highly selective and potent, covalent BTK inhibitor with a promising pharmacological and favorable safety profile, which could allow for maximising efficacy with the goal of achieving complete MS disease control
- The REMODEL I and II studies would provide clinical and paraclinical data by assessing the efficacy, safety, and tolerability of remibrutinib compared with teriflunomide in patients with RMS
- These studies will support regulatory approval worldwide for remibrutinib as a potential new oral treatment for patients with this disabling disease

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INTRODUCTION

- Inhibition of Bruton's tyrosine kinase (BTK), a cytoplasmic tyrosine kinase and member of the tyrosine protein kinase (TEC) family, results in reduced activation of B cells and innate immune cells[1]
  - This offers an alternative mechanism to modulate immune regulatory networks and related neuroinflammation via inhibition of B cells and myeloid cells[1]
- BTK inhibitors are a novel class of therapies that target B cells and innate immune cells, preventing inflammation and potential disease progression without depleting B cells in multiple sclerosis (MS)[2–4]
- Remibrutinib is a potent, highly selective, covalent BTK inhibitor with a promising pharmacological and safety profile

OBJECTIVE

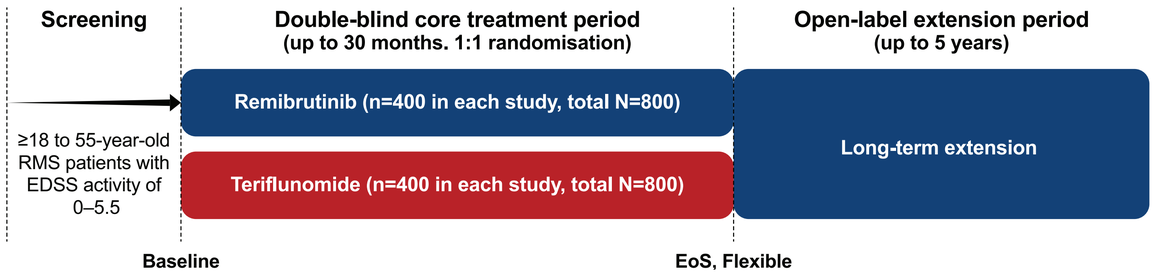
- To present the design of the REMODEL I and II Phase 3 trials, which aim to evaluate the efficacy, safety, and tolerability of remibrutinib versus teriflunomide in patients with relapsing MS (RMS)

METHODS

Study Design

- REMODEL I and II studies consist of an initial double-blind core part followed by an open-label extension
- An adaptive design with flexible study duration will enable completion of the core part after the collection of a pre-specified number of relapse and disability progression events
- A futility interim analysis is planned based on pooled 6-month magnetic resonance imaging (MRI) data (new/newly enlarging T2 lesions) from a subset of participants

Randomised, double-blind, double-dummy, active comparator-controlled, fixed-dose, parallel-group, event-driven multicentre studies



EDSS, Expanded Disability Status Scale; EoS, end of study; N, total number of patients; n, number of patients; RMS, relapsing multiple sclerosis.

Key Inclusion and Exclusion Criteria

Key inclusion criteria

- Male or female participants aged 18 to 55 years (inclusive) at screening
- Diagnosis of RMS according to the 2017 revised McDonald diagnostic criteria[5]
- RMS as defined by Lublin et al (2014)[6]
- At least: 1 documented relapse within the previous year, OR 2 documented relapses within the previous 2 years prior to screening, OR 1 active gadolinium enhancing (Gd+) lesion in the 12 months prior to screening
- Expanded Disability Status Scale (EDSS) score of 0–5.5 (inclusive) at screening and randomisation
- Neurologically stable within 1 month prior to screening and randomisation (including no MS relapse)

Key exclusion criteria

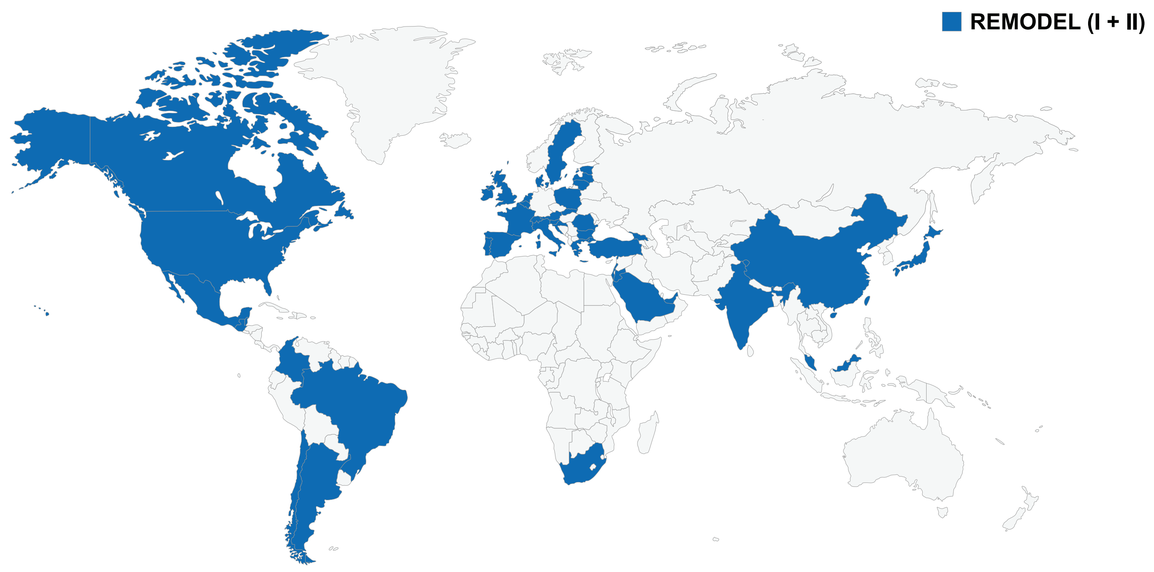
- Diagnosis of primary progressive MS (PPMS) according to the 2017 revised McDonald diagnostic criteria[5]
- Disease duration of >10 years in participants with an EDSS score of ≤2 at screening
- History of clinically significant central nervous system (CNS) disease other than MS
- History of malignancy of any organ system in past 5 years
- Active clinically significant systemic bacterial, viral, parasitic, or fungal infections
- Significant bleeding risk or coagulation disorders
- Have received any live or live attenuated vaccines within 6 weeks prior to randomisation
- Pregnant or nursing (lactating) female participants or women of childbearing potential unless using a highly effective method of contraception

Study Endpoints

Primary endpoint	• Annualised relapse rate
Key secondary endpoints	• 3-month and 6-month confirmed disability progression • Number of new or enlarging T2 lesions on MRI per year • Total number of Gd+ T1 lesions per MRI scan • NfL concentration in serum • Percentage of participants with NEDA-3

MRI, magnetic resonance imaging; NEDA, no evidence of disease activity; NfL, neurofilament light chain.

Participating Countries*



REMODEL I and II studies are currently recruiting patients

Planned Enrolment ~40 countries ~1600 patients

*Listed countries may be pending to receive local HA, EC, and IRB approval. For more details on participating countries and study sites, please visit the clinicaltrials.gov website.
EC, Ethics Committee; HA, health authority; IRB, Institutional Review Board.

Disclosures

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, and UCB Biopharma. **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. **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. **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 by 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 AstraZeneca, 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. **Brett Loop**, **Alit Bhatt**, **Brian Hunter**, **Ying Zhang**, **Rajesh Karan**, **Roman Willi**, and **Bernd Kieseier** are employees of Novartis. **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 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.

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