Phase 3 REMODEL I/II Trials: Effectiveness, Safety, and Tolerability of Remibrutinib in Patients with Relapsing Multiple Sclerosis

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REMODEL I/II: Background and objective

- Inhibition of Bruton's tyrosine kinase (BTK), a cytoplasmic tyrosine kinase and member of the TEC kinase 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 MS[2,3,4]
- Remibrutinib is a potent, highly selective, covalent BTK inhibitor with a short plasma half-life, and a promising pharmacological and safety profile

Objective

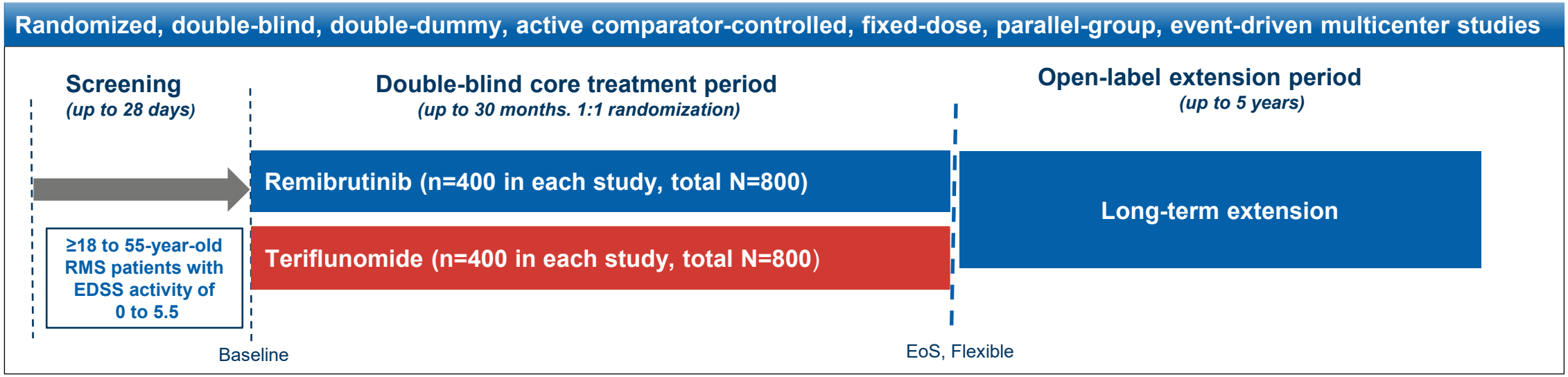
To present the design of the REMODEL I and II Phase 3 trials, which aim to evaluate the efficacy, safety, and tolerability of remibrutinib versus teriflunomide in patients with RMS

BTK, Bruton's tyrosine kinase; MS, multiple sclerosis; RMS, relapsing MS; TEC, tyrosine-protein kinase.

1. Steinmaurer A et al. *Curr Pharm Des*. 2021;27;1–8; 2. Gruber RC et al. Poster Presented at American Academy of Neurology, April 17-22, 2021. S25.003; 3. Reich DS et al. *Lancet Neurol*. 2021;20(9):729–38;
4. Montalban X et al. *N Engl J Med*. 2019;380(25):2406-2417.

REMODEL I/II: 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
- An interim analysis is planned based on pooled 6-month MRI data (new/newly enlarging T2 lesions) from a subset of participants



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

REMODEL I/II: Key inclusion and exclusion criteria

Key inclusion criteria

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

Key exclusion criteria

- Diagnosis of PPMS according to the 2017 revised McDonald diagnostic criteria[1]
- Disease duration of >10 years in participants with an EDSS score of ≤2 at screening
- History of clinically significant 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 randomization
- Pregnant or nursing (lactating) female participants or women of childbearing potential unless using highly effective method of contraception

CNS, central nervous system; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; MS, multiple sclerosis; PPMS, primary-progressive MS; RMS, relapsing MS.

1. Thompson AJ et al. *Lancet Neurol*. 2018;17:162–73;2; 2. Lublin FD et al. *Neurology*. 2014;83:278–86.

REMODEL I/II: Study endpoints

Primary endpoint

- Annualized relapse rate

Key secondary endpoints

- 3-month & 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

Other secondary endpoints

- Time-to-first confirmed relapse
- Time to 6mCDI on EDSS
- Change from baseline in the SDMT
- Time to 6mCDW in T25FW or 9HPT
- PROs: FSIQ-RMS, GAD-7, PHQ-9, BPI-SF, HUI-III, MSIS-29

6mCDI, 6-month confirmed disability improvement; 6mCDW, 6-month confirmed disability worsening; 9HPT, 9-Hole Peg Test; BPI-SF, Brief Pain Inventory-Short Form; EDSS, Expanded Disability Status Scale; FSIQ-RMS, Fatigue Symptoms and Impacts Questionnaire–Relapsing Multiple Sclerosis; GAD-7, Generalized Anxiety Disorder; Gd+, gadolinium-enhancing; HUI, Health Utilities Index; MRI, magnetic resonance imaging; MSIS, Multiple Sclerosis Impact Scale; NEDA, no evidence of disease activity; NfL, neurofilament light chain; PHQ, Patient Health Questionnaire; PROs, Patient-reported Outcomes; SDMT, symbol digit modalities test; T25FW, Timed 25-Foot Walk Test.

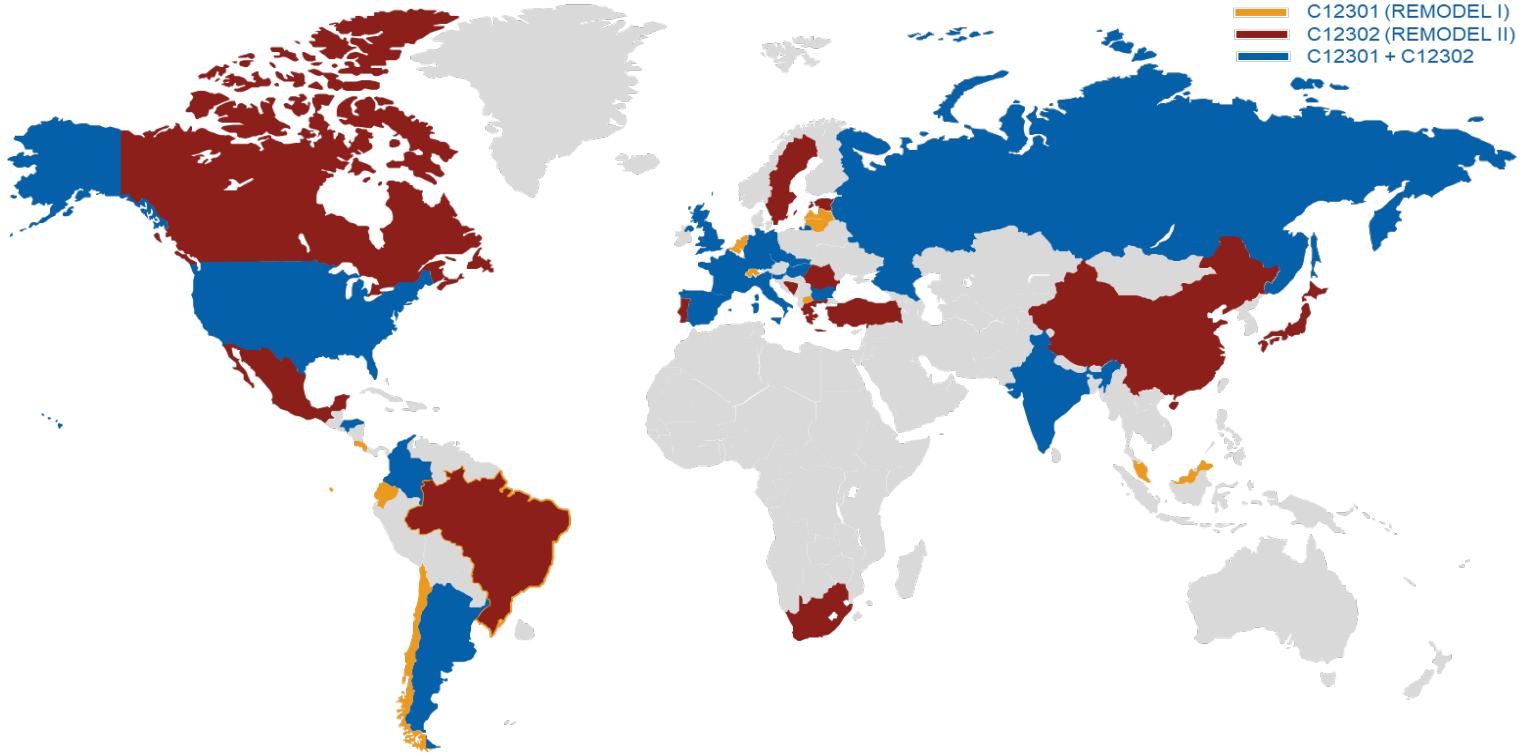
REMODEL I/II: Participating countries*

REMODEL I and II studies are currently recruiting patients

Planned enrollment

~40 countries

~1600 patients



*Listed countries have expressed interest to participate, and may be pending to receive local HA, EC, and IRB approval. For more details on enrollment sites, please visit clinicaltrials.gov website.
Argentina, Belgium, Brazil, Bulgaria, Canada, Chile, China, Colombia, Croatia, Czech Republic, Estonia, France, Germany, Greece, Guatemala, Hong Kong, Hungary, India, Italy, Lithuania, Latvia, Malaysia, Mexico, Netherlands, Poland, Portugal, Romania, Russia, South Africa, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, UK, US.

Conclusions

- Remibrutinib is a highly selective, covalent BTK inhibitor with a promising pharmacological profile and favorable potency, selectivity and safety which could allow for maximizing efficacy with the goal to achieve 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 relapsing multiple sclerosis
- These studies will support regulatory approval worldwide for remibrutinib as a potential new oral treatment for patients with this disabling disease

BTK, Bruton's tyrosine kinase; MS, multiple sclerosis.