Frexalimab in Relapsing Multiple Sclerosis and Non-Relapsing Secondary Progressive Multiple Sclerosis: Design of Phase 3 FREXALT and FREVIVA Trials

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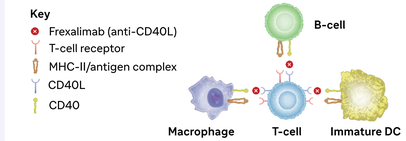
Stephen Krieger[1], Patrick Vermersch[2], Tanuja Chitnis[3], Yang Mao-Draayer[4], Cristina Granziera[5,6], Eva Kubala Havrdova[7], Xavier Montalban[8], Elena Gargaun[9], Stephane Saubadu[9], Philippe Truffinet[9], Heinz Wiendl[10], Gavin Giovannoni[11]

[1]Corinne Goldsmith Dickinson Center for Multiple Sclerosis, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [2]Univ. Lille, Inserm UI172 LilNCog, CHU Lille, FHU Precise, Lille, France; [3]Mass General Brigham Pediatric MS Center, Massachusetts General Hospital, Boston, MA, USA; [4]Multiple Sclerosis Center of Excellence, Oklahoma Medical Research Foundation, Oklahoma City, OK, USA; [5]Translational Imaging in Neurology (ThINk) Basel, Department of Biomedical Engineering, Faculty of Medicine, University Hospital Basel and University of Basel, Basel, Switzerland; [6]Neurologic Clinic and Policlinic, MS Center and Research Center for Clinical Neuroimmunology and Neuroscience Basel (RC2NB), University Hospital Basel and University of Basel, Basel, Switzerland; [7]Department of Neurology, First Faculty of Medicine, Charles University, Prague, Czech Republic; [8]Multiple Sclerosis Centre of Catalonia, Department of Neurology, Vall d'Hebron University Hospital, Barcelona, Spain; [9]Sanofi, Gentilly, France; [10]Department of Neurology with Institute of Translational Neurology, University Hospital and University of Münster, Münster, Germany; [11]Queen Mary University of London, London, UK

BACKGROUND

- The CD40/CD40L co-stimulatory pathway is an upstream regulator of both adaptive and innate immune responses, and has been linked to multiple sclerosis (MS) pathophysiology[1–4]
- Frexalimab targets the upstream biology of MS by blocking the CD40/CD40L co-stimulatory pathway, which is important for immune cell crosstalk that affects activation of adaptive (T and B cells) and innate immune cells (macrophages/microglia), without causing lymphocyte depletion[2–6]
- In the Phase 2 trial in participants with relapsing MS (RMS; NCT04879628), frexalimab showed favorable safety and efficacy:[7]
  - 89% reduction in new gadolinium-enhancing (Gd+) T1 lesions in the 1200-mg every four weeks (Q4W) intravenous arm vs. pooled placebo at week 12
  - Continued reduction in number of both T1 and T2 lesions over 48 weeks[8]
- The efficacy and safety of frexalimab is being investigated in two global Phase 3 trials:
  - **FREXALT** (NCT06141473) evaluates frexalimab vs. teriflunomide in participants with RMS[9]
  - **FREVIVA** (NCT06141486) evaluates frexalimab vs. placebo in participants with non-relapsing secondary progressive MS (nrSPMS)[10]

Figure 1. Inhibition of CD40/CD40L interaction with frexalimab



Frexalimab, a second-generation anti-CD40L humanized IgG1 monoclonal antibody, is derived from a first-generation antibody, with 2 major modifications:

1. Affinity maturation of the variable region
2. Mutations in the Fc region to prevent binding to the Fc receptor, FcγRIIa, which is broadly expressed on platelets, monocytes, and macrophages

DC, dendritic cell; IgG1, immunoglobulin G1; MHC, major histocompatibility complex.

OBJECTIVE

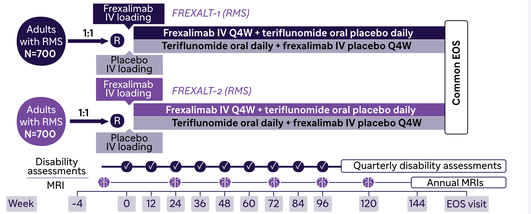
- To describe the study design of Phase 3 **FREXALT** and **FREVIVA** trials

METHODS

FREXALT CLINICAL TRIAL

- **Trial design:** Two independent (FREXALT-1 and FREXALT-2) Phase 3, randomized, double-blind, double-dummy, active-controlled, parallel group, event-driven (6-month composite confirmed disability worsening [cCDW] pooled across studies) trials comparing efficacy and safety of frexalimab with teriflunomide in participants with RMS
- **Treatment duration:** 20–40 months

Figure 2. FREXALT trial design



EOS, end of study; IV, intravenous; MRI, magnetic resonance imaging; Q4W, every 4 weeks; R, randomization; RMS, relapsing multiple sclerosis.

Key inclusion criteria

- Age 18–55 years
- Diagnosis of RMS[11]
- Expanded Disability Status Scale (EDSS) score ≤5.5 at first visit
- One of the following prior to screening:
  - ≥1 relapse in previous year
  - ≥2 relapses in previous 2 years
  - ≥1 Gd+ T1 lesion in previous year

Key exclusion criteria

- Diagnosis of primary progressive MS (PPMS)[11] or SPMS without activity[12]
- Medical conditions that would adversely impact study participation
- History or presence of disease that can mimic MS symptoms

Primary endpoint

- **ARR** assessed by protocol-defined adjudicated relapses

Secondary endpoints

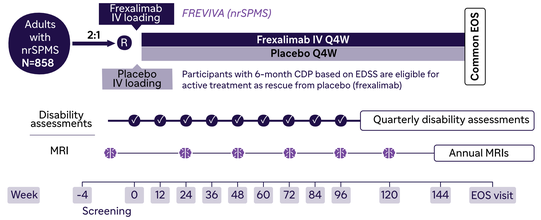
- **Key secondary endpoint:** Time to onset of **6-month cCDW** defined by the composite of
  - Increase from the baseline **EDSS score** of ≥1.5 points when the baseline is 0, or ≥1.0 point when the baseline is 0.5 to 5.0, or ≥0.5 point when the baseline is ≥5.5 (or)
  - Increase of ≥20% from the baseline time in **9HPT** (or)
  - Increase of ≥20% from the baseline time in **T25FW test**
- Time to onset of:
  - **cCDW, confirmed over 3 months**
  - Individual cCDW components confirmed over 3 or 6 months
  - CDI[a], confirmed over 6 months
- Progression independent of relapse activity[b]
- New and/or enlarging **T2 lesions**
- New Gd+ **T1 lesions** per scan
- Change in **brain volume loss** at EOS Month 6
- Change in cognitive function by **SDMT**
- Change in quality of life by **MSIS-29v2 questionnaire** scores and **PROMIS-Fatigue MS-8a** scores
- Safety
- Changes in **plasma NfL** and **serum immunoglobulin** levels
- **Plasma concentration** of frexalimab over time

[a]Defined as decrease from the baseline EDSS score of ≥1.0 or ≥ 0.5 points when the baseline is ≥2 to ≤5.5 or >5.5 points, respectively.
[b]Defined as the time to onset of 6-month cCDW, defined by either no prior relapse or an onset more than 90 days after the start date of the last investigator-reported relapse.
9HPT, 9-hole peg test; ARR, annualized relapse rate; CDI, confirmed disability improvement; cCDW, composite confirmed disability worsening; EDSS, Expanded Disability Status Scale; EOS, end of study; MSIS-29v2, Multiple Sclerosis Impact Scale 29-item version 2; NfL, neurofilament light chain; PROMIS, Patient Reported Outcome Measurement Information System; SDMT, Symbol Digit Modalities Test; T25FW, timed 25-foot walk.

FREVIVA CLINICAL TRIAL

- **Trial design:** Phase 3, randomized, double-blind, placebo-controlled, parallel group, event-driven (6-month composite confirmed disability progression [cCDP]) trial comparing efficacy and safety of frexalimab with placebo in participants with nrSPMS
- **Treatment duration:** 27–51 months

Figure 3. FREVIVA trial design



CDP, confirmed disability progression; EDSS, expanded disability status scale; EOS, end of study; IV, intravenous; MRI, magnetic resonance imaging; nrSPMS, non-relapsing secondary progressive multiple sclerosis; Q4W, every 4 weeks; R, randomization.

Key inclusion criteria

- Age 18–60 years
- Current diagnosis of SPMS[12]
- Previous diagnosis of RRMS[11]
- EDSS score 3.0–6.5
- Documented disability progression in previous 12 months as analyzed by an Eligibility Adjudication Committee
- No clinical relapses for at least 24 months

Key exlusion criteria

- Medical conditions that would adversely impact study participation
- History or presence of disease that can mimic MS symptoms

Primary endpoint

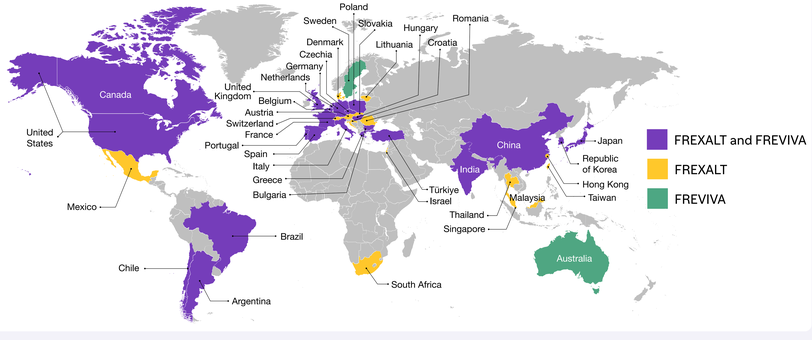
- Time to onset of **6-month cCDP** Defined by the composite of:
  - Increase from the baseline **EDSS score** of ≥1.0 point when baseline is <5.5, or ≥0.5 point if baseline is ≥5.5 (or)
  - Increase of ≥20% from the baseline time in **9HPT** (or)
  - Increase of ≥20% from the baseline time in **T25FW test**

Secondary endpoints

- Time to onset of each of:
  - **cCDP,** confirmed over 3 months
  - **CDP,** confirmed over 3 or 6 months[a]
  - **CDI,** confirmed over 6 months[b]
- New and/or enlarging **T2 lesions**
- Change in **brain volume loss** at EOS vs. Month 6
- Change in cognitive function by **SDMT**
- Change in quality of life by **MSIS-29v2 questionnaire** scores and **PROMIS Fatigue MS-8a** scores
- **ARR**, assessed by protocol-defined adjudicated relapses
- Safety
- Changes in **plasma NfL** and **serum immunoglobulin levels**
- **Plasma concentration** of frexalimab over time

[a]Increase from the baseline EDSS score of ≥1.0 point when the baseline is <5.5, or ≥0.5 point when the baseline is ≥5.5.
[b]Decrease from the baseline EDSS score of ≥1.0 or ≥0.5 points when baseline is ≤5.5 or >5.5 points, respectively.
9HPT, 9-hole peg test; ARR, annualized relapse rates; cCDP, composite confirmed disability progression; CDI, confirmed disability improvement; EDSS, expanded disability status scale; EOS, end of study; MSIS-29v2, Multiple Sclerosis Impact Scale 29-item version 2; NfL, neurofilament light chain; PROMIS, Patient-Reported Outcome Measurement Information System; SDMT, Symbol Digit Modalities Test; T25FW, timed 25-foot walk.

Figure 4. World map depicting planned enrollment for both trials



CONCLUSIONS

- Frexalimab regulates the activation and function of adaptive and innate immunity, and has the potential to address both acute and chronic neuroinflammation in MS
- Positive Phase 2 findings provide the rationale for targeting CD40L in MS and support further development of frexalimab in Phase 3 trials as a potential high-efficacy, non-lymphocyte-depleting therapy
- These Phase 3 trials will assess efficacy and safety of frexalimab:
  - **FREXALT**, in participants with RMS, a population in which disability accumulation remains a significant unmet need
  - **FREVIVA**, in participants with nrSPMS, for whom no approved treatment options currently exist
- Enrollment of both trials has started and recruitment is ongoing

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References: 1. Elgueta R, et al. *Immunol Rev.* 2009;229:152–72; **2.** Aarts SABM, et al. *J Neuroinflammation.* 2017;14(105):1–14; **3.** Karnell JL, et al. *Adv Drug Deliv Rev.* 2019;141:92–103; **4.** Fadul CE, Mao-Draayer Y, et al. *Neurol Neuroimmunol Neuroinflamm.* 2021;8(6):e1096; **5.** Pucino V, et al. *Lancet Rheumatol.* 2020;2(5):e292–e301; **6.** Mathur RK, et al. *Trends Parasitol.* 2006;22(3):117–22; **7.** Vermersch P, et al. *N Engl J Med.* 2024;30(7):589–600; **8.** Giovannoni G, et al. *Neurology.* 2024;102:S31.007; **9.** ClinicalTrials.gov. NCT06141473; **10.** ClinicalTrials.gov. NCT06141486; **11.** Thompson AJ, et al. *Lancet Neurol.* 2018;17(2):162–73; **12.** Lublin FD, et al. *Neurology.* 2014;83(3):278–86.

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