# Phase 2 Efficacy and Safety of Frexalimab: 6-Month Results of a Novel CD40L Inhibitor in Relapsing Multiple Sclerosis

P275

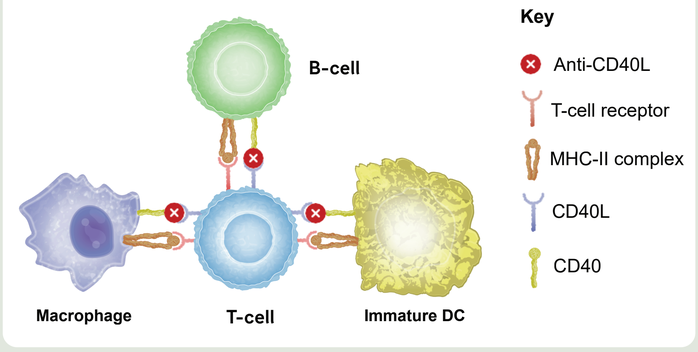
*Patrick Vermersch*[1], *Cristina Granziera*[2,3], *Yang Mao-Draayer*[4], *Gary Cutter*[5], *Oleksandr Kalbus*[6], *Ivan Staikov*[7], *Michal Dufek*[8], *Stephane Saubadu*[9], *Raphael Bejuit*[9], *Philippe Truffinet*[9], *Biljana Djukic*[10], *Erik Wallstroem*[10], *Gavin Giovannoni*[11]

[1]*Univ. Lille, Inserm U1172 LilNCog, CHU Lille, FHU Precise, Lille, France;* [2]*Translational Imaging in Neurology (ThINk) Basel, Department of Biomedical Engineering, Faculty of Medicine, University Hospital Basel and University of Basel, Basel, Switzerland;* [3]*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;* [4]*Department of Neurology, Autoimmunity Center of Excellence, University of Michigan Medical Center, Michigan, United States;* [5]*Department of Biostatistics, UAB School of Public Health, Birmingham, Alabama, United States;* [6]*Department of Neurology, Dnipro State Medical University, Dnipro, Ukraine;* [7]*Clinic of Neurology and Sleep Medicine, Acibadem City Clinic University Hospital Tokuda, Sofia, Bulgaria;* [8]*1st Department of Neurology, St. Anne's University Hospital, Brno, Czech Republic;* [9]*Sanofi, Chilly-Mazarin, France;* [10]*Sanofi, Cambridge, MA, United States;* [11]*Queen Mary University of London, London, United Kingdom*

## *INTRODUCTION AND OBJECTIVE*

- The CD40/CD40L costimulatory pathway regulates initiation of both adaptive and innate immune responses. Clinical and pathological evidence suggest a key role of CD40/CD40L in the development and progression of multiple sclerosis (MS), with possible links to peripheral tolerance and the Epstein-Barr virus[1-4]
- Frexalimab is the first second-generation anti-CD40L humanized immunoglobulin-1 monoclonal antibody being evaluated for treatment of MS, and has the potential to block T-cell interactions with CD40-expressing cells, including B-cells and innate antigen-presenting cells, such as dendritic cells and macrophages (**Figure 1**)[3-6]
- Frexalimab modifies T- and B-cell activation and innate immune cell function, without depleting lymphocytes, and may provide durable disease modification and/or reinstate tolerance
- In the phase 2 randomized controlled trial (NCT04879628), frexalimab met the primary endpoint with the high-dose treatment arm showing an 89% reduction in new gadolinium-enhancing (Gd+) lesions at Week (W) 12 (during the double-blind period), compared with the pooled placebo arm in participants with relapsing MS (RMS)[8]
- Here, we report the efficacy and safety data at W24 from the ongoing open-label part of the frexalimab phase 2 trial in participants with RMS

**Figure 1. Inhibition of the CD40/CD40L interaction[7]**

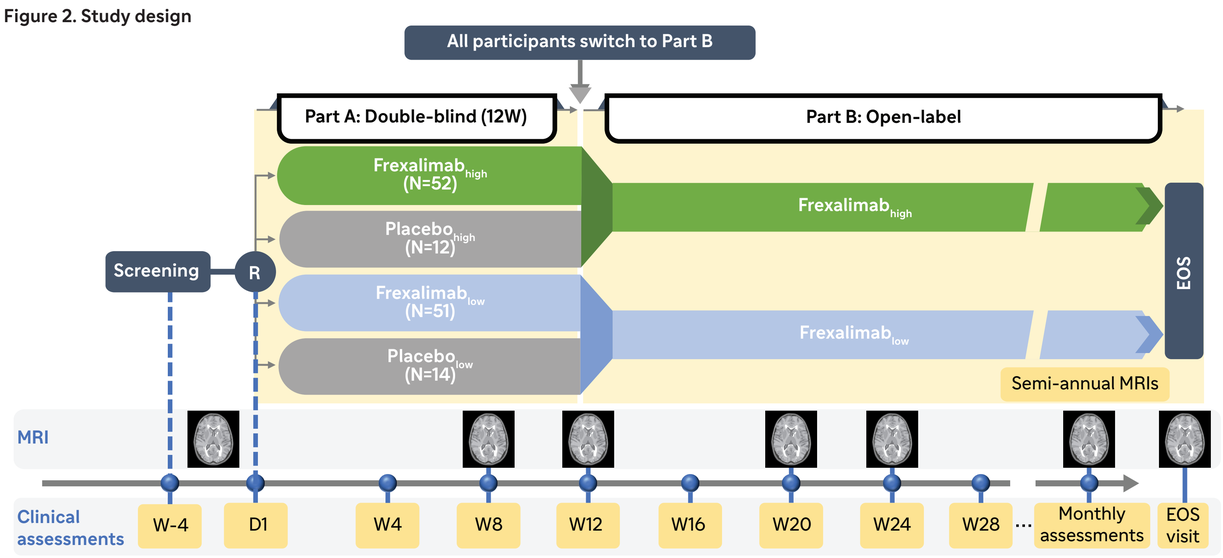



DC, dendritic cell; MHC, major histocompatibility complex.

## *METHODS*

- Participants aged 18-55 years were randomized (4:4:1:1) to receive high-dose frexalimab (frexalimab$_{high}$; N=52), low-dose frexalimab (frexalimab$_{low}$; N=51), or matching placebos (high-dose placebo [placebo$_{high}$], N=12; low-dose placebo [placebo$_{low}$], N=14)
- Participants who completed the 12-week double-blind period (Part A) entered the open-label extension period (Part B; **Figure 2**)
- In Part B, participants in the frexalimab groups continued receiving their frexalimab dose (frexalimab$_{high}$ or frexalimab$_{low}$) in an open-label fashion; participants in the placebo groups switched to respective frexalimab treatment (either high-dose [placebo$_{high}$/frexalimab$_{high}$] or low-dose [placebo$_{low}$/frexalimab$_{low}$])

**Figure 2. Study design**




D, day; EOS, end of study; MRI, magnetic resonance imaging; N, number of participants; R, randomization; W, week.

**Key Study Endpoints and Assessments**

- Safety: Incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and adverse events of special interest (AESIs) at W24
- Magnetic resonance imaging (MRI) endpoints: Number of new Gd+ T1 lesions at W24, number of new or enlarging T2 lesions at W24, and change in total number of Gd+ T1 lesions from baseline at W24
  - For all MRI-derived endpoints, a blinded review was performed at a central facility (NeuroRx)
- Plasma-based circulating biomarkers of inflammatory activity and neuroaxonal damage: Change from baseline in plasma neurofilament light chain (NfL) and chemokine (C-X-C motif) ligand 13 (CXCL13) levels at W24
- All efficacy and safety endpoints were evaluated with descriptive statistics and presented by initial treatment groups in the open-label extension population, which consisted of all participants who received at least one dose of study intervention during the open-label extension phase

## *RESULTS*

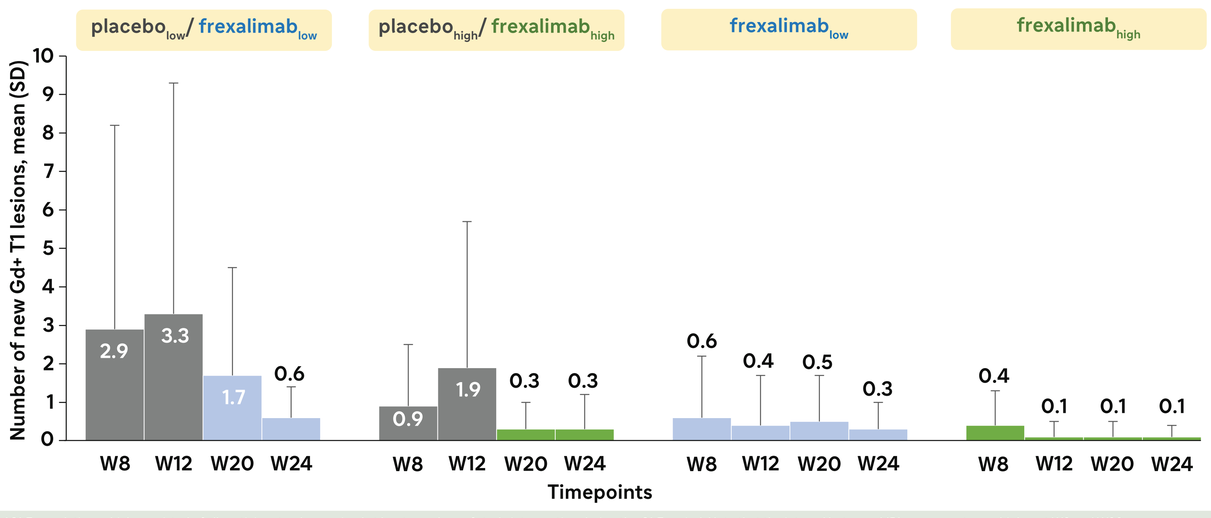
**Participants**

- Of 129 randomized participants, 125 (97%) completed part A and entered the open-label part B
  - As of Jan 19, 2023 (W24 for the last participant randomized), 118 (91.5%) participants continued receiving treatment in the open-label period
  - Reasons for open-label study discontinuation: 1 (0.8%) participant discontinued due to AE, 3 (2.3%) participants discontinued due to the Ukraine war, and 4 (3.1%) participants withdrew from the study
- At baseline, the mean (standard deviation) age of enrolled participants was 36.6 (9.4) years; 66% were women[8]

**MRI Outcomes**

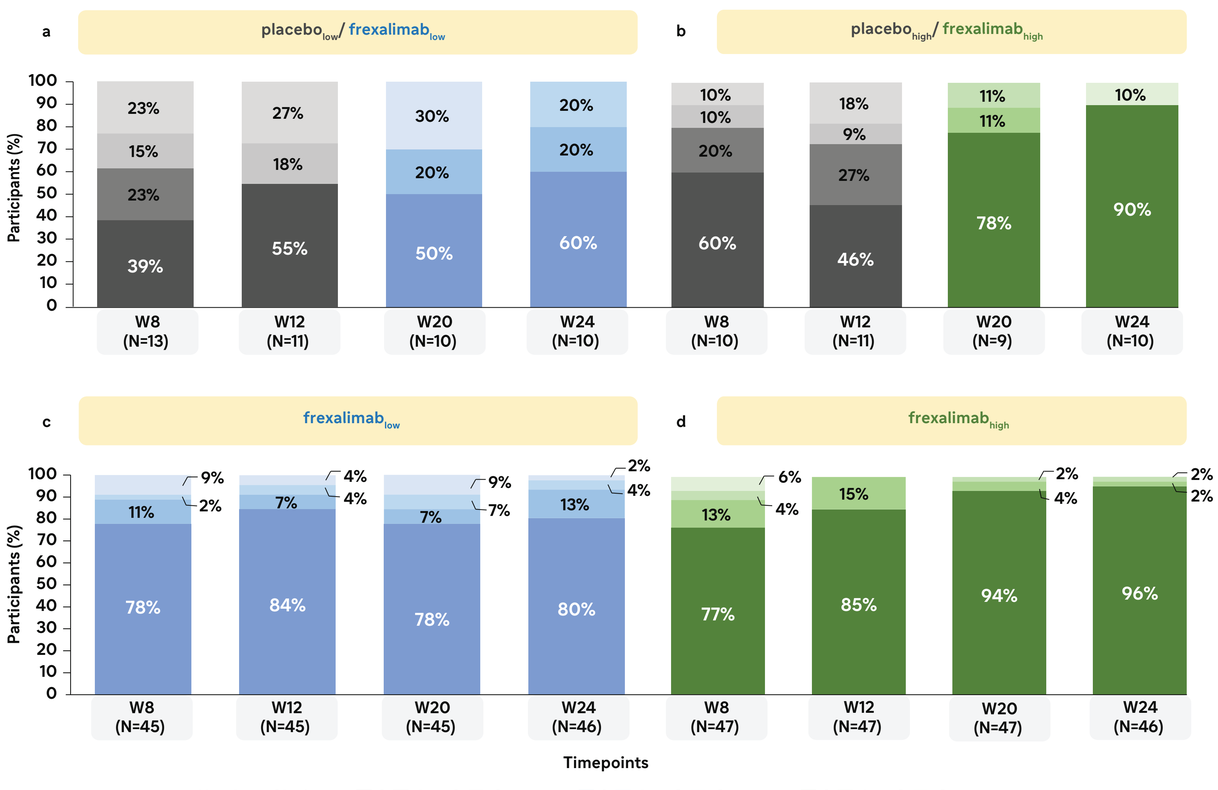
- At W24, there was a rapid and marked reduction in the number of new Gd+ T1 lesions (mean [SD]) in participants who switched from placebo to frexalimab treatment at W12 (placebo$_{low}$/frexalimab$_{low}$: 3.3 [6.0] at W12 and 0.6 [0.8] at W24; placebo$_{high}$/frexalimab$_{high}$: 1.9 [3.8] at W12 and 0.3 [0.9] at W24; **Figure 3**)
  - Upon switching to corresponding frexalimab treatments, 60% of participants originally in the placebo$_{low}$ group and 90% originally in the placebo$_{high}$ group were free of new Gd+ lesions at W24 (**Figure 4**)
- Number of lesions further decreased in participants who continued receiving frexalimab (frexalimab$_{low}$: 0.4 [1.3] at W12 and 0.3 [0.7] at W24; frexalimab$_{high}$: 0.1 [0.4] at W12 and 0.1 [0.3] at W24; **Figure 3**)
  - Among participants who continued receiving frexalimab treatments, 80% in the frexalimab$_{low}$ group and 96% in the frexalimab$_{high}$ group were free of new Gd+ T1 lesions at W24 (**Figure 4**)

**Figure 3. Number of new Gd+ T1 lesions over time***




*OLE population, which consisted of all participants who received at least one dose of study intervention during the OLE period. Note that the interval between MRI assessments was higher at W8 and W20.
Gd+, gadolinium-enhancing; MRI, magnetic resonance imaging; OLE, open-label extension; SD, standard deviation; W, week.

**Figure 4. Proportion of participants with no new Gd+ T1 lesions over time***




*OLE population, which consisted of all participants who received at least one dose of study intervention during the OLE period.
Gd+, gadolinium-enhancing; OLE, open-label extension; W, week.

## *CONCLUSIONS*

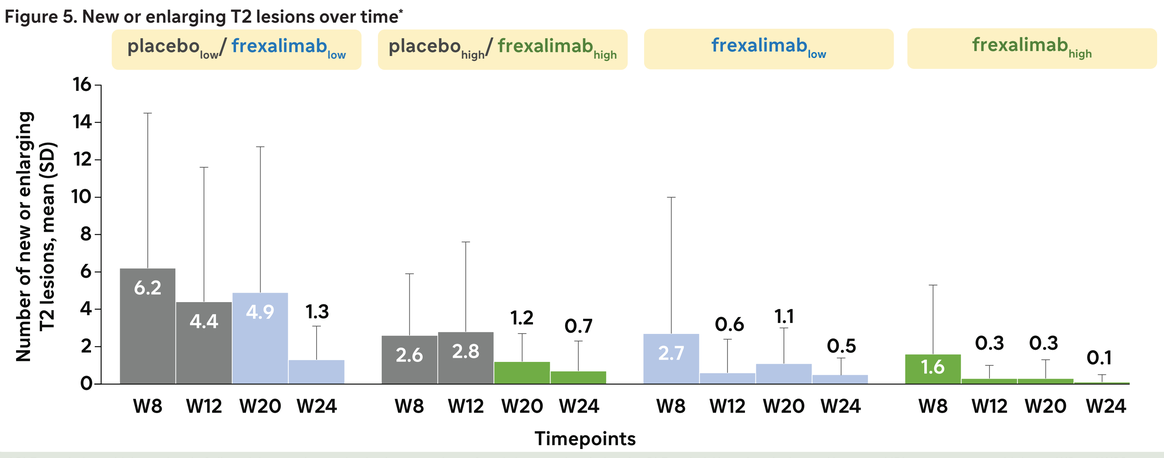
- Frexalimab treatment led to a sustained reduction of disease activity over 24 weeks as measured by MRI, with 96% of participants in the frexalimab$_{high}$ group and 80% in the frexalimab$_{low}$ group being free of new Gd+ T1 lesions at W24
- At W24, there was a rapid and marked reduction in the number of lesions in the placebo group participants upon switching to frexalimab$_{high}$ treatment at 12 weeks
- Frexalimab treatment was well-tolerated and had an acceptable safety profile over 24 weeks; no new safety signals were observed in the placebo group participants who switched to frexalimab treatment or in those who remained on frexalimab after 12 weeks
- These findings strengthen the rationale for targeting CD40L in MS and support further development of frexalimab as a potential high-efficacy, non-lymphocyte-depleting therapy

Copies of this poster obtained through Quick Response (QR) Code are for personal use only

## *RESULTS (CONT..)*

- At W24, the number of new or enlarging T2 lesions (**Figure 5**) and total Gd+ T1 lesions (data not shown) reduced rapidly in the placebo group participants upon switching to frexalimab treatment at W12, while it remained low through W24 for participants continuing to receive frexalimab

**Figure 5. New or enlarging T2 lesions over time***

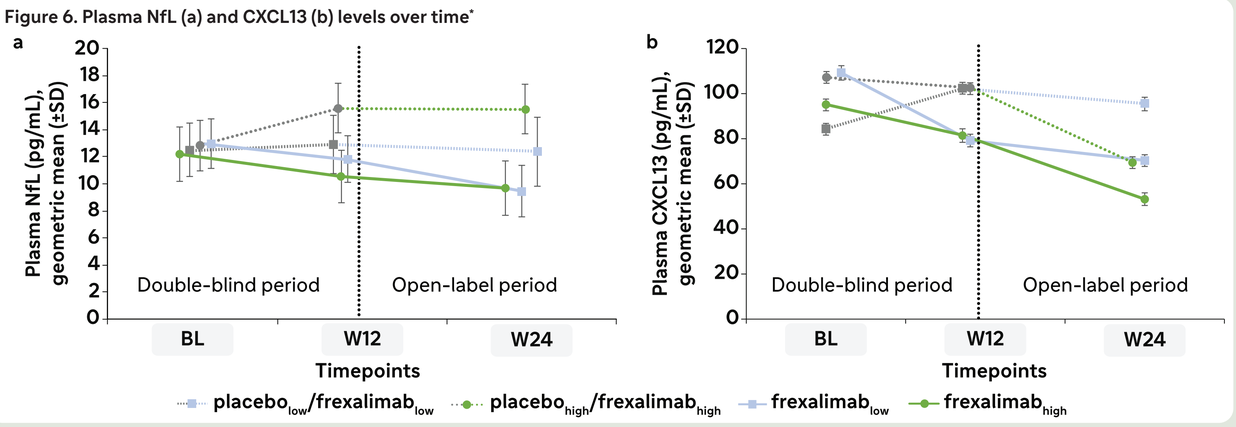



*OLE population, which consisted of all participants who received at least one dose of study intervention during the OLE period. Note that the interval between MRI assessments was higher at W8 and W20.
MRI, magnetic resonance imaging; OLE, open-label extension; SD, standard deviation; W, week.

**Blood Biomarkers, Lymphocytes, and Immunoglobulin G**

- The reductions in plasma NfL and CXCL13 levels were sustained over W24 in participants who remained on frexalimab treatment (**Figure 6**)

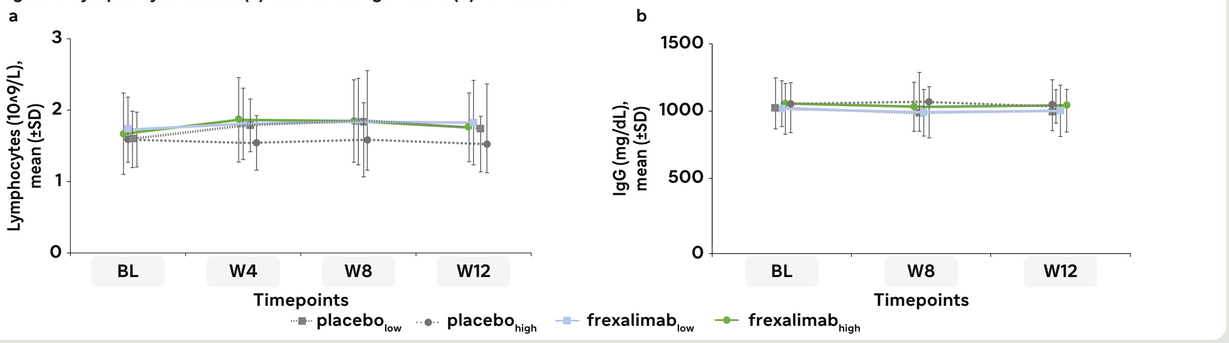
**Figure 6. Plasma NfL (a) and CXCL13 (b) levels over time***




*OLE population, which consisted of all participants who received at least one dose of study intervention during the OLE period.
BL, baseline; CXCL13, chemokine (C-X-C motif) ligand 13; NfL, neurofilament light chain; OLE, open-label extension; SD, standard deviation; W, week.

- Lymphocyte counts and immunoglobulin G (IgG) levels remained stable over 12 weeks† (**Figure 7**)

**Figure 7. Lymphocyte counts (a)* and serum IgG levels (b)** over time**




*OLE population, which consisted of all participants who received at least one dose of study intervention during the OLE period. **Safety population, which consisted of all randomized participants who received at least one dose (regardless of the amount) of study intervention.
†W24 data was not available at the time of poster preparation and will be presented in the future.
BL, baseline; IgG, immunoglobulin G; OLE, open-label extension; SD, standard deviation; W, week.

**Safety**

- The safety data for the 12-week double-blind period has been previously presented[8]
  - Frexalimab treatment was generally safe and well-tolerated during the 12-week double-blind period; no serious or severe TEAEs were reported
  - The most common TEAE observed during the double-blind period was COVID-19; five uncomplicated cases of COVID-19 (all mild to moderate in intensity) were observed in the frexalimab$_{low}$ group
- Here, we report the safety data in the open-label period from W12 until the cut-off at W24 for the last participant randomized (median [range] follow up duration was 48.7 [23-78] weeks)
  - 60 of 125 (48%) participants reported at least one TEAE; the most common AEs observed were similar to those reported during the double-blind period, including COVID-19‡, nasopharyngitis, and headache **(Table 1)**
  - No new safety signals were observed for placebo group participants who switched to the frexalimab treatments

**Table 1. Summary of adverse events (open-label period until the cut-off at W24 from baseline)***

| Participants, n (%) | Placebo$_{low}$/ frexalimab$_{low}$ (N=14) | Placebo$_{high}$/ frexalimab$_{high}$ (N=12) | Frexalimab$_{low}$ (N=49) | Frexalimab$_{high}$ (N=50) |
|---|---|---|---|---|
| Any AE | 8 (57.1) | 7 (58.3) | 22 (44.9) | 23 (46.0) |
| Any SAE | 0 | 0 | 0 | 2 (4.0)§ |
| AE leading to death | 0 | 0 | 0 | 0 |
| AE leading to permanent treatment discontinuation | 0 | 1 (8.3) | 0 | 0 |
| AESI† | 1 (7.1) | 1 (8.3) | 3 (6.1) | 9 (18.0) |
| Most common AEs (≥10% in any group) | | | | |
| COVID-19‡ | 1 (7.1) | 1 (8.3) | 2 (4.1) | 5 (10.0) |
| Nasopharyngitis | 0 | 0 | 1 (2.0) | 5 (10.0) |
| Headache | 0 | 1 (8.3) | 7 (14.3) | 4 (8.0) |

*OLE population, which consisted of all participants who received at least one dose of study intervention during the OLE period; the same participant may have experienced more than one AE during the OLE period.
§Lower limb fracture (n=1) and cholecystectomy due to gallbladder wall thickening of mild intensity, which recovered immediately on treatment (n=1). †Treatment-emergent AESIs included ALT increase (n=2; with no associated bilirubin elevation, which recovered on treatment), viral gastroenteritis, pruritic rash, and urticaria (n=1 each), and COVID-19 (n=10, including one asymptomatic case of COVID-19). ‡All COVID-19 cases were considered non-serious and recovered on treatment. One case of COVID-19 in the placebo$_{high}$/frexalimab$_{high}$ group led to treatment discontinuation.
AE, adverse event; AESI, adverse event of special interest; ALT, alanine aminotransferase; COVID-19, coronavirus disease 2019; OLE, open-label extension; SAE, serious adverse event; W, week.

**Disclosures**

**Patrick Vermersch:** Received honoraria and consulting fees (Biogen, Sanofi, Novartis, Teva, Merck, Roche, Imcyse, AB Science, and BMS-Celgene) and research support (Novartis, Sanofi, and Roche). **Cristina Granziera:** The University Hospital Basel (USB), as the employer of C.G., has received the following fees which were used exclusively for research support: (i) advisory boards and consultancy fees from Actelion, Novartis, Sanofi, GeNeuro, Hoffmann La Roche, and Siemens; (ii) speaker fees from Biogen, Hoffmann La Roche, Teva, Novartis, Merck, Jannsen Pharmaceuticals, and Sanofi; (iii) research grants: Biogen, Sanofi, Hoffmann La Roche, and GeNeuro. **Yang Mao-Draayer:** Received consulting and/or speaker fees (Acorda, Bayer Pharmaceutical, Biogen, Bristol Myers Squibb [Celgene], Chugai, EMD Serono, Genentech-Roche, Janssen, Novartis, Sanofi, and Teva) and research support (Chugai, Genentech-Roche, NIAID Autoimmune Center of Excellence, NIH NINDS, Novartis, PCORI, and Sanofi). **Gary Cutter:** Data and Safety Monitoring Boards: Applied Therapeutics, AI therapeutics, AMO Pharma, Astra-Zeneca, Avexis Pharmaceuticals, Biolinerx, Brainstorm Cell Therapeutics, Bristol Meyers Squibb/Celgene, CSL Behring, Galmed Pharmaceuticals, Green Valley Pharma, Horizon Pharmaceuticals, Immunic, Karuna Therapeutics, Mapi Pharmaceuticals LTD, Merck, Mitsubishi Tanabe Pharma Holdings, Opko Biologics, Prothena Biosciences, Novartis, Regeneron, Sanofi, Reata Pharmaceuticals, Teva Pharmaceuticals, NHLBI (Protocol Review Committee), University of Texas Southwestern, University of Pennsylvania, Visioneering Technologies, Inc. Consulting or Advisory Boards: Alexion, Antisense Therapeutics, Biogen, Clinical Trial Solutions LLC, Entelexo Biotherapeutics, Inc., Sanofi, Genentech, GW Pharmaceuticals, Immunic, Immunosis Pty Ltd, Klein-Buendel Incorporated, Merck/Serono, Novartis, Perception Neurosciences, Protalix Biotherapeutics, Regeneron, Roche, and SAB Biotherapeutics. Dr. Cutter is employed by the University of Alabama at Birmingham, and President of Pythagoras, Inc. a private consulting company located in Birmingham. **Oleksandr Kalbus:** Received honoraria and/or consulting and/or speaker fees (Sanofi, Roche, Genentech, Merck, Novartis, GeNeuro, Bristol Myers Squibb [Celgene], Mapi Pharmaceuticals LTD, VielaBio Inc., and Teva). **Ivan Staikov:** Received travel funding and/or consultant fees and/or speaker honoraria (Sanofi, Ewopharma-Biogen, Shire, Gedeon-Richter, TEVA, Boehringer Ingelheim, Pfizer, Bayer, F. Roche, Mylan, Polpharma, Penumbra, Adapt, Merck, Gerot Lannach, Medochemie, Novartis, Viatris, and Nobel Pharma). **Michal Dufek:** Study coordinator (Sanofi). **Stephane Saubadu, Raphael Bejuit, Philippe Truffinet, Biljana Djukic, Erik Wallstroem:** Employees of Sanofi (may hold shares and/or stock options in the company). **Gavin Giovannoni:** Received compensation over the last five years for receiving research support or serving as a consultant or speaker (AbbVie, Actelion, Atara Bio, Biogen, Canbex, Celgene, EMD Serono, Japanese Tobacco, Sanofi, Genentech, GlaxoSmithKline, GW Pharma, Merck, Novartis, Roche, Synthon BV, and Teva).

**Presented at the 9th Joint ECTRIMS-ACTRIMS Meeting; Milan, Italy; 11-13 October 2023**

**Acknowledgments**

This Phase 2 trial (NCT04879628) is funded by Sanofi. Sanofi is developing frexalimab (SAR441344) under an exclusive license from ImmuNext Inc. The authors and Sanofi thank the participants and their families for their involvement in the frexalimab Phase 2 randomized controlled trial. The authors would also like to thank the investigators for their contribution to this study. Medical writing support for this poster was provided by Akshada Deshpande, and was reviewed by Reema Patel and Svend Geertsen, of Sanofi.

**References**

1. Elgueta R, et al. Immunol Rev. 2009;229:152-72.
2. Imadome K, et al. Proc Natl Acad Sci U S A. 2003;100:7836-40.
3. Aarts SABM, et al. J Neuroinflammation. 2017;14(105):1–14.
4. Karnell JL, et al. Adv Drug Deliv Rev. 2019;141:92–103.
5. Fadul CE, et al. Neurol Neuroimmunol Neuroinflamm. 2021;8(6):e1096.
6. Pucino V, et al. Lancet Rheumatol. 2020;2(5):e292–e301.
7. Mathur RK, et al. Trends Parasitol. 2006;22(3):117–22.
8. Vermersch P, et al. IJMSC. 2023; 25(2):1 (LB02).