# Safety and Efficacy of Frexalimab in Participants with Relapsing Multiple Sclerosis: 2.5-Year Results From the Phase 2 Open-label Extension

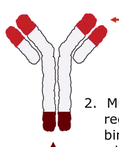
24-28 Ottobre 2025
Padova Congress
55° CONGRESSO SOCIETÀ ITALIANA DI NEUROLOGIA

Claudio Gasperini[1], Patrick Vermersch[2], Cristina Granziera[3], Yang Mao-Draayer[4], Gary Cutter[5], Oleksandr Kalbus[6], Ivan Staikov[7], Michal Dufek[8], Xavier Montalban[9], Stephen Krieger[10], Heinz Wiend[11,12], Stephane Saubadu[13], Xiaodong Luo[14], Brendan Smyth[15], Biljana Djukic[16], Philippe Truffinet[17], Erik Wallstroem[18], Gavin Giovannoni[16]

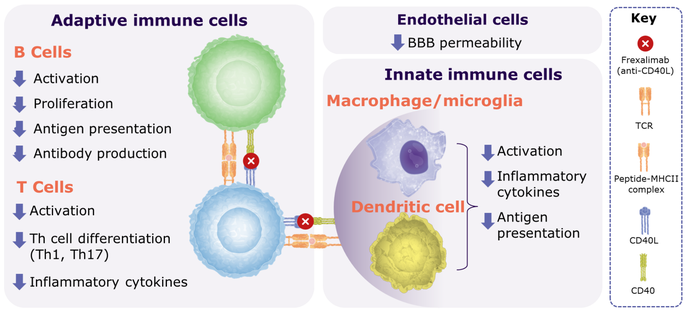
*[1]Multiple Sclerosis Center, Neurology Unit S. Camillo-Forlanini Hospital, Rome, Italy. [2]University of Lille, Inserm U1172 LilNCog, CHU Lille, FHU Precise, Lille, France, [3]Translational Imaging in Neurology (ThINk) Basel, Department of Biomedical Engineering, Faculty of Medicine; Neurologic Clinic and Policlinic, MS Center and Research Center for Clinical Neuroimmunology and Neuroscience Basel (RC2NB), University Hospital Basel and University of Basel, Basel, Switzerland, [4]Autoimmunity Center of Excellence, Oklahoma Medical Research Foundation, Oklahoma City, OK, United States, [5]Department of Biostatistics, UAB School of Public Health, Birmingham, AL, 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]First Department of Neurology, St. Anne's University Hospital, Faculty of Medicine, Masaryk University, Brno, Czech Republic, [9]Multiple Sclerosis Centre of Catalonia, Department of Neurology, Vall d'Hebron University Hospital, Barcelona, Spain, [10]Corinne Goldsmith Dickinson Center for Multiple Sclerosis, Icahn School of Medicine at Mount Sinai, New York, NY, United States, [11]Department of Neurology and Neurophysiology, University of Freiburg, Freiburg, Germany, [12]Brain & Mind Institute, University of Sydney, Sydney, Australia, [13]Sanofi, Gentilly, France, [14]Sanofi, Morristown, NJ, United States, [15]Sanofi, Cambridge, MA, United States, [16]Queen Mary University of London, London, United Kingdom; Study Group: Frexalimab Phase 2 Study Group*

## *Frexalimab: proposed mechanism of action*

**Frexalimab**, a **second-generation anti-CD40L humanized IgG1 mAb**, is derived from a first-generation Ab, with 2 major modifications:



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




- The CD40/CD40L costimulatory pathway regulates **adaptive and innate** immune responses and is implicated in pathogenesis of MS[1-3]
- By inhibiting this pathway, frexalimab modifies **T and B cell activation** and innate immune cell function (**macrophage/microglia and dendritic cell**), without depleting lymphocytes[4,5]

Ab, antibody; BBB, blood-brain barrier; CD40, cluster of differentiation 40; CD40L, CD40 ligand; FcγRIIa, fragment crystallizable gamma receptor IIa; IgG, immunoglobulin G; mAb, monoclonal Ab;MHC, major histocompatibility complex; MS, multiple sclerosis; TCR, T-cell receptor; Th, T helper; W, week.

1. Gerritse K, et al. *Proc Natl Acad Sci USA*. 1996;93:2499–2504; 2. Howard LM, et al. *J Clin Invest*. 1999;103:281–290; 3. t'Hart BA, et al. *J Neuroimmunol.* 2005;163:31–39; 4. Vermersch P, et al. *N Engl J Med*. 2024;390(7):589–600; 5. Vermersch P, et al. *Curr Treat Options Neurol.* 2025;27(7):1–11.

## *Frexalimab met primary endpoint in phase 2 trial*

In the 12-week DBP of a Phase 2 trial in participants with relapsing MS (NCT04879628), frexalimab showed **favorable safety and efficacy**[1]

**89%** reduction ($p$=0.0004) in **new Gd+ T1 lesions** (primary endpoint) in frexalimab$_{1200mg/IV}$ Q4W arm vs pooled placebo at W12[1]

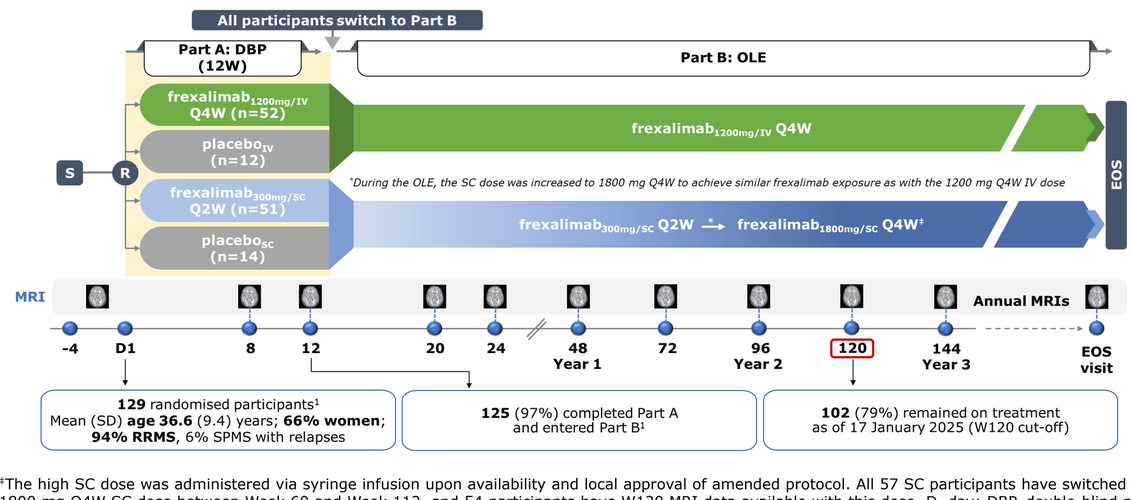
**Sustained reduction** in number of lesions was noted **over 2 years** in the OLE with frexalimab treatment[2]

DBP, double-blind period; Gd+, gadolinium enhancing; IV, intravenous; MS, multiple sclerosis; OLE, open-label extension; Q4W, every 4 weeks; W, week. 1. Vermersch P, et al. *N Engl J Med*. 2024;390(7):589–600; 2. Vermersch P, et al. *Neurology*. 2025;1785(104):7_Supplement_1. doi: 10.1212/WNL.0000000000208742.

## OBJECTIVE

**To report safety and efficacy of frexalimab at W120 (2.5 years) in the OLE of phase 2 trial in participants with relapsing MS**

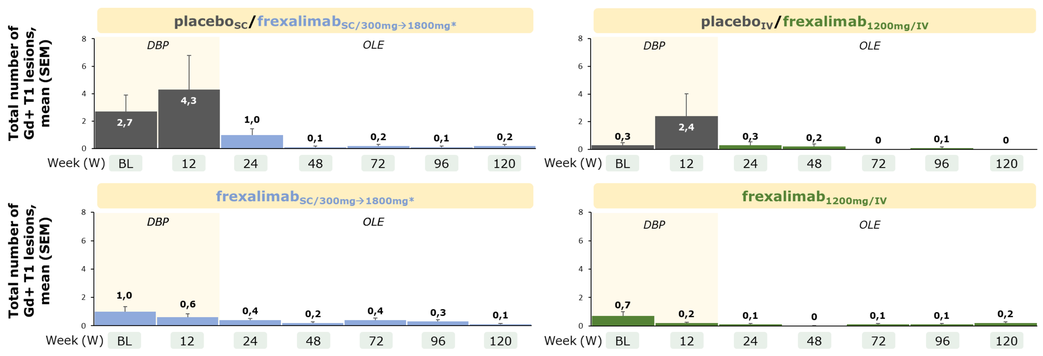
## *Trial design and participant disposition*




‡The high SC dose was administered via syringe infusion upon availability and local approval of amended protocol. All 57 SC participants have switched to the 1800 mg Q4W SC dose between Week 60 and Week 112, and 54 participants have W120 MRI data available with this dose. D, day; DBP, double-blind period; EOS, end of study; IV, intravenous; MRI, magnetic resonance imaging; NfL, neurofilament light chain; OLE, open-label extension; Q2W, every 2 weeks; Q4W, every 4 weeks; R, randomisation; RRMS, relapsing-remitting multiple sclerosis; S, screening; SC, subcutaneous; SD, standard deviation; SPMS, secondary progressive multiple sclerosis; W, week. 1. Vermersch P, et al. *N Engl J Med.* 2024;390(7):589–600.

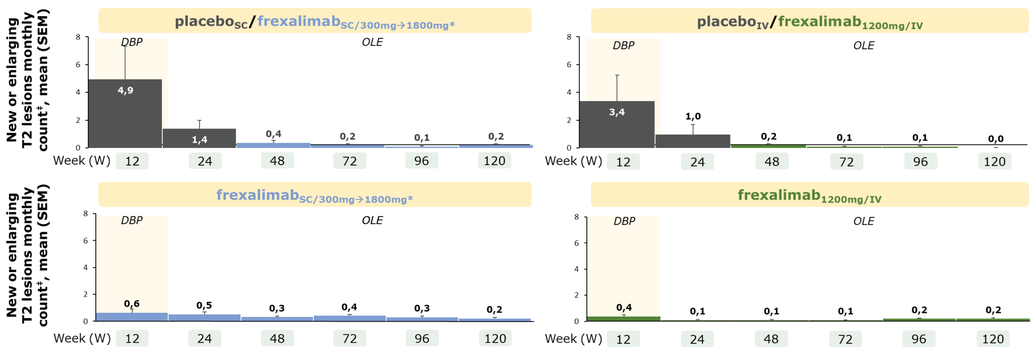
# RESULTS

## *Total Number of Gd+ T1 Lesions remained low through 120 weeks*



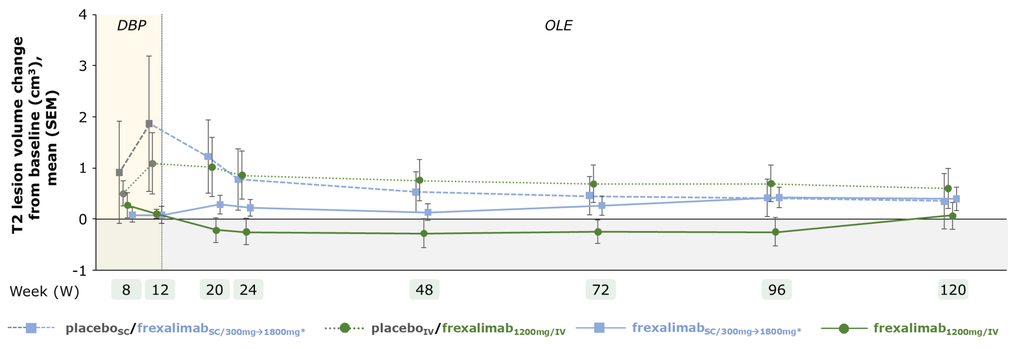

*During the OLE, the SC dose was increased to 1800 mg Q4W to achieve similar frexalimab exposure as with the 1200 mg Q4W IV dose.
BL, baseline; DBP, double-blind period; Gd+, gadolinium enhancing; IV, intravenous; OLE, open-label extension; Q4W, every 4 weeks; SC, subcutaneous; SEM, standard error of the mean; W, week.

## *New or enlarging T2 lesions monthly count remained low through 120 weeks*




*During the OLE, the SC dose was increased to 1800 mg Q4W to achieve similar frexalimab exposure as with the 1200 mg Q4W IV dose.
‡New or enlarging T2 lesions monthly count was calculated as lesion count divided by the interscan interval in months.
DBP, double-blind period; IV, intravenous; OLE, open-label extension; Q4W, every 4 weeks; SC, subcutaneous; SEM, standard error of the mean; W, week.

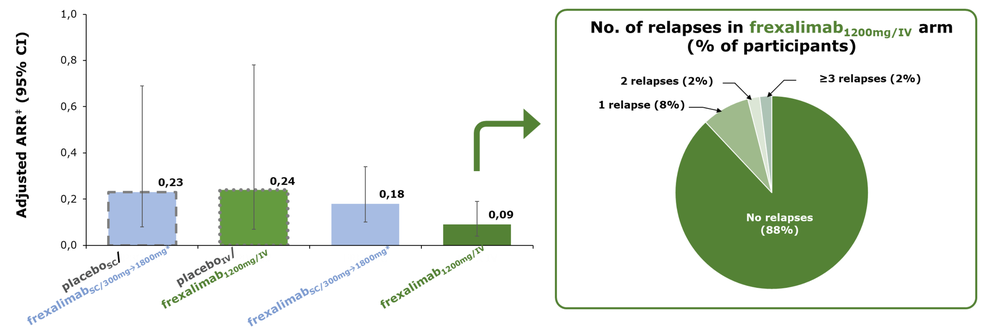
## *Change in T2 lesion volume from baseline remained low through 120 weeks*




*During the OLE, the SC dose was increased to 1800 mg Q4W to achieve similar frexalimab exposure as with the 1200 mg Q4W IV dose. DBP, double-blind period; IV, intravenous; OLE, open-label extension; Q4W, every 4 weeks; SC, subcutaneous; SEM, standard error of the mean; W, week.

**Funded by Sanofi**

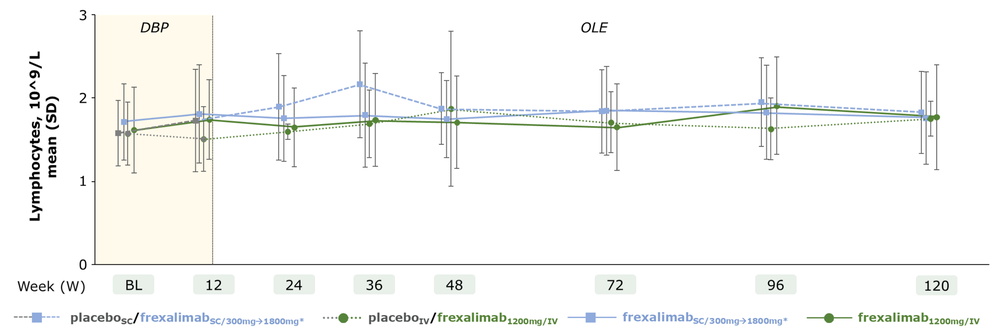
## *Annualised Relapse Rate at Week 120*




*During the OLE, the SC dose was increased to 1800 mg Q4W to achieve similar frexalimab exposure as with the 1200 mg Q4W IV dose. ‡Estimated using a negative binomial regression model including the total number of confirmed relapses (as per the protocol) with onset over considered period (baseline–W120 visit date) as response variable and initial treatment as covariate, with log transformed standardised period duration included as an offset variable. ARR, annualised relapse rate; CI, confidence interval; IV, intravenous; OLE, open-label extension; Q4W, every 4 weeks; SC, subcutaneous; W, week.

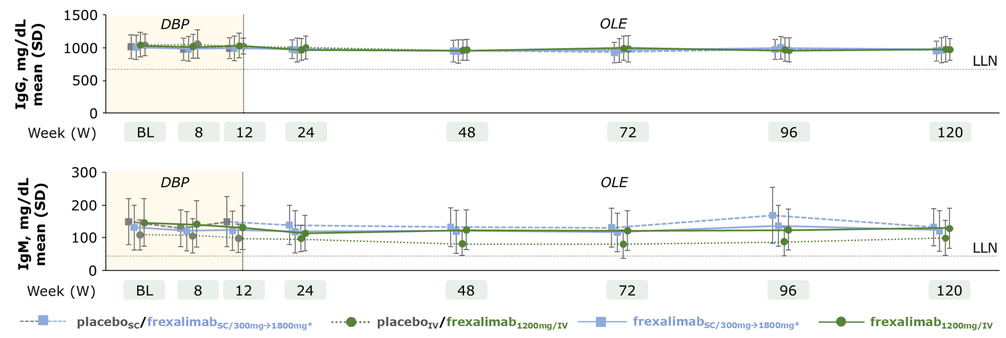
- ARR (baseline–W120) was low (0.09 [95% CI, 0.04–0.19]) in the frexalimab$_{1200mg/IV}$ arm
- 88% of participants remained relapse-free from baseline up to their W120 visit
- Mean EDSS scores remained low and stable through 120 weeks

## *Lymphocyte counts remained stable over 120 weeks*




*During the OLE, the SC dose was increased to 1800 mg Q4W to achieve similar frexalimab exposure as with the 1200 mg Q4W IV dose. BL, baseline; DBP, double-blind period; IV, intravenous; OLE, open-label extension; Q4W, every 4 weeks; SC, subcutaneous; SD, standard deviation; W, week.

## *IgG and IgM levels showed stability or marginal decrease over 120 weeks*




Note: LLN values for IgG and IgM, respectively are: 700 mg/dL and 40 mg/dL. *During the OLE, the SC dose was increased to 1800 mg Q4W to achieve similar frexalimab exposure as with the 1200 mg Q4W IV dose. BL, baseline; DBP, double-blind period; Ig, immunoglobulin; IV, intravenous; LLN, lower limit of normal; OLE, open-label extension; Q4W, every 4 weeks; SC, subcutaneous; SD, standard deviation; W, week.

## *AEs From W12 Until W120 Cut-off*

| Participants, n (%) | placeboSC/ frexalimabSC/300mg→1800mg* (n=14) | placeboIV/ frexalimab1200mg/IV (n=12) | frexalimabSC/300mg→1800mg* (n=49) | frexalimab1200mg/IV (n=50) |
|---|---|---|---|---|
| Any AE | 13 (93) | 9 (75) | 42 (86) | 36 (72) |
| Serious AEs | 1 (7)# | 0 | 2 (4)¥ | 7 (14)‡ |
| AEs leading to death | 0 | 0 | 0 | 0 |
| AEs leading to permanent treatment discontinuation | 0 | 1 (8)¶ | 0 | 3 (6)§ |
| Most common AEs (≥10% in any arm)ᴖ | | | | |
| COVID-19** | 3 (21) | 1 (8)¶ | 6 (12) | 9 (18) |
| Nasopharyngitis | 3 (21) | 2 (17) | 8 (16) | 8 (16) |
| Headache | 0 | 1 (8) | 8 (16) | 6 (12) |
| Back pain | 0 | 2 (17) | 5 (10) | 4 (8) |

*During the OLE, the SC dose was increased to 1800 mg Q4W to achieve similar frexalimab exposure as with the 1200 mg Q4W IV dose. #Serious AE of epilepsy occurred in a participant with history of adolescent focal epilepsy and was deemed unrelated to treatment.¥Serious AEs of pneumonia (n=1) and tibia fracture (n=1).‡Serious AEs of Escherichia pyelonephritis, influenza, pneumonia, papillary thyroid cancer, gallbladder enlargement, and lower limb fracture (n=1 each) were reported; one additional event of lower limb fracture was not coded at the time of cut-off. §AEs of papillary thyroid cancer, ALT increase, and pulmonary embolism (n=1 each) led to permanent treatment discontinuation. **All COVID-19 (n=19) cases were of mild to moderate intensity, of which one COVID-19 event in the placeboIV/frexalimab1200mg/IV arm¶ led to permanent treatment discontinuation due to protocol rules.
ᴖDosing greater than protocol-defined threshold was reported using AE process (IV doses: increase of at least 30% of the dose to be administered or the dose is administered in less than 30 min; SC doses: at least twice the intended dose within 8 days); 19 such participants who had accidental overdose were excluded from this table.

## *AEs of Special Interest*

| Participants, n (%) | placeboSC/ frexalimabSC/300mg→1800mg* (n=14) | placeboIV/ frexalimab1200mg/IV (n=12) | frexalimabSC/300mg→1800mg* (n=49) | frexalimab1200mg/IV (n=50) |
|---|---|---|---|---|
| AEs of special interest | 3 (21) | 1 (8) | 8 (16) | 11 (22) |
| COVID-19¥ | 3 (21) | 1 (8) | 6 (12) | 9 (18) |
| ALT increase | 0 | 0 | 0 | 2 (4)# |
| Pulmonary embolism | 0 | 0 | 0 | 1 (2)§ |
| Pneumonia | 0 | 0 | 1 (2) | 0 |
| Pregnancy | 0 | 0 | 2 (4)ᴖ | 0 |

*During the OLE, the SC dose was increased to 1800 mg Q4W to achieve similar frexalimab exposure as with the 1200 mg Q4W IV dose. ¥Total 19 participants had COVID-19 events; all events were of mild to moderate intensity, of which one COVID-19 event in the placeboIV/frexalimab1200mg/IV arm led to permanent treatment discontinuation due to protocol rules. #During the OLE period, 2 participants in the frexalimab1200mg/IV arm experienced an increase in ALT levels. One participant had recurring, isolated ALT level increases, leading to permanent treatment discontinuation. The first increase (9x ULN) occurred at 6 months after starting treatment and resolved while the participant continued to receive frexalimab. Subsequent increases were noted at 19 months (9x ULN) and 22 months (6x ULN) after treatment initiation, all deemed non-serious and with bilirubin levels within normal limits. The second participant in the frexalimab1200mg/IV arm had an isolated ALT increase at 5 months (5x ULN) after starting the treatment, which resolved within a month, while the participant continued to receive frexalimab; this event was considered not related to frexalimab. §A participant with heterozygous prothrombin mutation [G20210A] and a history of atrial fibrillation had an incidental pulmonary embolism following influenza A, after 1 year and 7 months of frexalimab treatment. This event was deemed unrelated to the treatment, led to permanent treatment discontinuation as per protocol, and the participant fully recovered.ᴖBoth participants withdrew from treatment as they intended to become pregnant.

# CONCLUSIONS

Frexalimab treatment resulted in a sustained **reduction of disease activity** over 2.5 years (W120), demonstrated by a low number of Gd+ T1 lesions and new/enlarging T2 lesions

**Clinical endpoints remained stable** over 2.5 years:
- Low frequency of relapses
- 88% participants relapse-free
- Stable EDSS scores

Frexalimab was **well-tolerated** through 2.5 years, with no new safety signals and **stable lymphocyte counts**

Phase 3 trials, FREXALT CLINICAL TRIAL (NCT06141473) and FREVIVA CLINICAL TRIAL (NCT06141486), are **actively recruiting** and will assess the efficacy and safety of frexalimab in people with RMS and nrSPMS, respectively

**Frexalimab continues to show favorable safety and sustained reduction in disease activity in people with RMS through 2.5 years, supporting its further development in Phase 3 trials as a potential high-efficacy, non-lymphocyte-depleting therapy**