Long-term Treatment Effect of Frexalimab on NfL and Plasma Biomarkers of Adaptive and Innate Immunity

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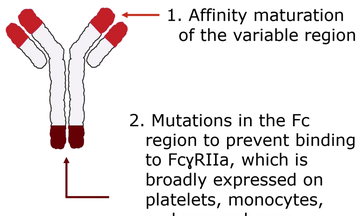
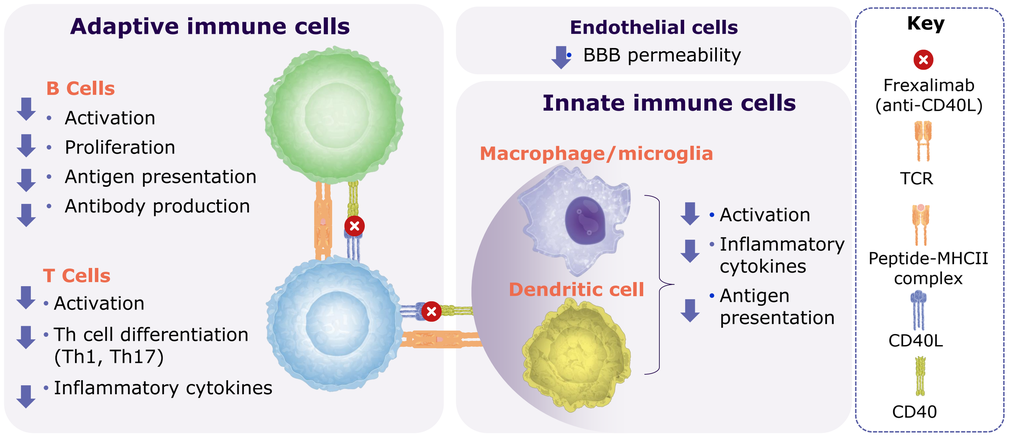
Frexalimab: proposed mechanism of action

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



- 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]

This was accompanied by **24%** and **21%** reductions in **NfL** and **CXCL13** levels, respectively, during the DBP[1], followed by a sustained effect in the OLE[2]

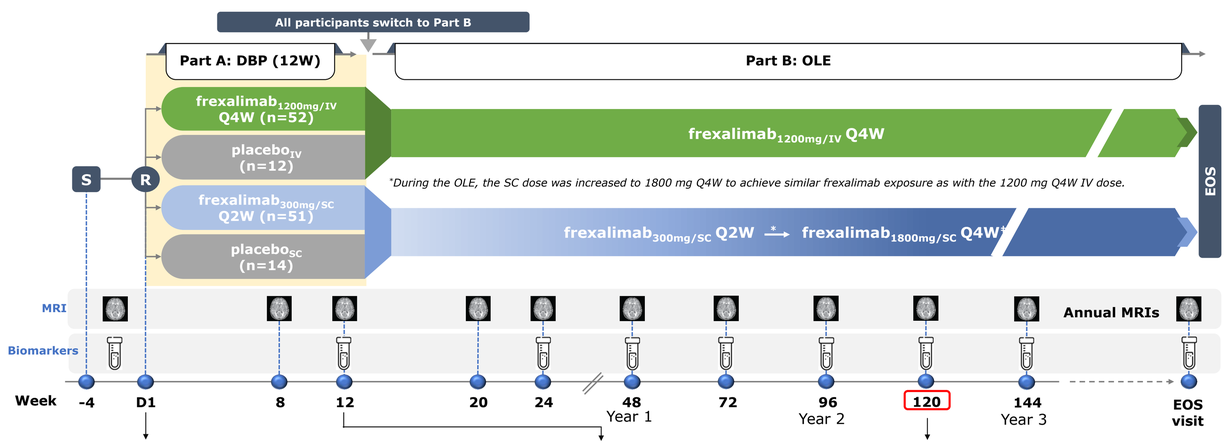
CXCL13, chemokine (C-X-C motif) ligand 13; DBP, double-blind period; Gd+, gadolinium-enhancing; IV, intravenous; MS, multiple sclerosis; NfL, neurofilament light chain; OLE, open-label extension; Q4W, every 4 weeks; W, week.

1. Vermersch P, et al. *N Engl J Med*. 2024;390(7):589-600; 2. Arnold DL, et al. Presented at the ECTRIMS 2025. Poster 830.

OBJECTIVE

To report frexalimab's treatment effects on plasma levels of NfL and immune cell biomarkers at 2.5 years (W120) in the OLE of Phase 2 trial

Trial design and participant disposition



129 randomised participants[1] Mean (SD) age **36.6** (9.4) years; **66% women**; 94% **RRMS**, 6% SPMS with relapses

125 (97%) completed Part A and entered Part B[1]

102 (79%) remained on treatment as of 17 January 2025 (W120 cut-off)

[‡]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.

Sample and data analysis

Sample analysis

- Plasma NfL and CXCL13 levels were analysed at baseline, W12, W24, W48, W72 and W120 using Quanterix Simoa NF-LIGHT™ assay and a Meso Scale Discovery assay, respectively
- Plasma sCD27, sTREM2, and CHI3L1 levels were measured at baseline, W12, W24, W48, W72, and W120 by ELISA

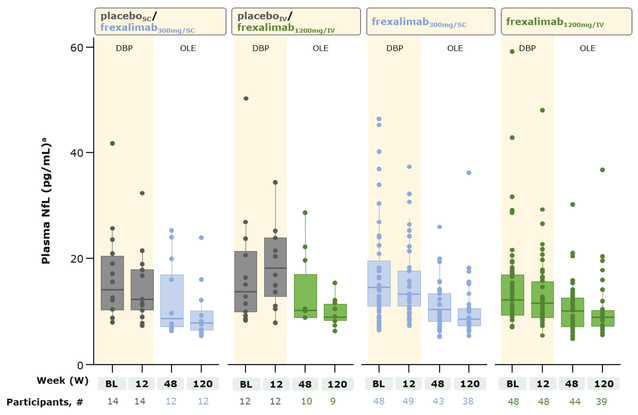
Data analysis

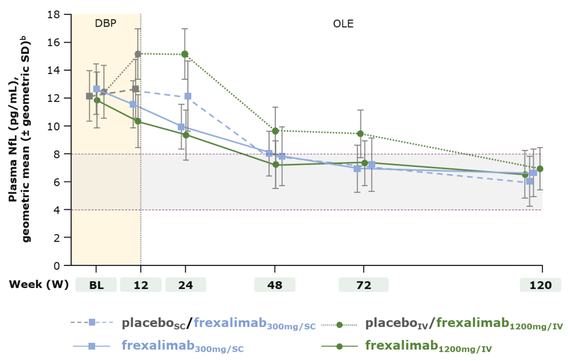
- Data are reported as geometric mean +/- standard deviation
- The differences from baseline were calculated and the results are summarized using percent (%) change of the geometric mean

CHI3L1, chitinase-3-like protein 1; CXCL13, chemokine (C-X-C motif) ligand 13; ELISA, enzyme-linked immunosorbent assay; NfL, neurofilament light chain; sCD27, soluble cluster of differentiation 27;
sTREM2, soluble triggering receptor expressed on myeloid cells; W, week.

RESULTS

Change in plasma NfL levels

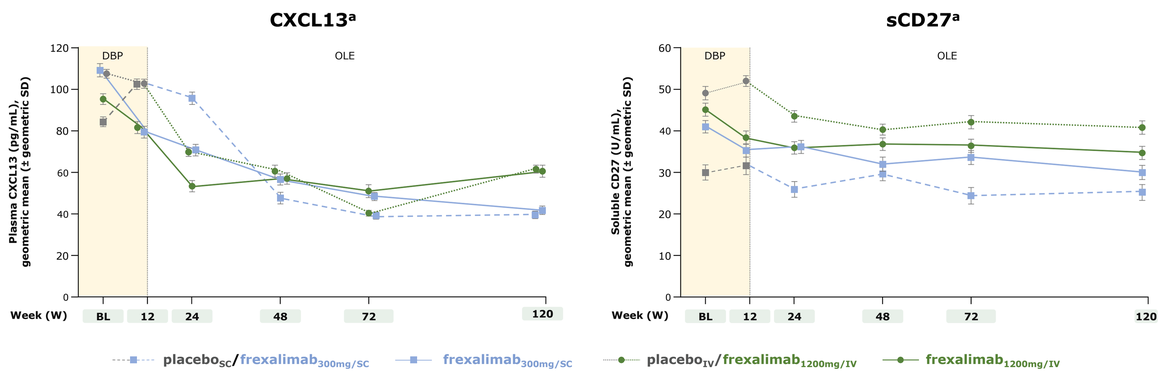




[a]Baseline-anchored z-scores were calculated, and any datapoints where z-score >3 were removed from visualization on the dot plot. Two datapoints were removed from the frexalimab $_{1200mg/IV}$ treatment arm.
[b]Participants per group at W120: placebo$_{SC}$/frexalimab$_{300mg/SC}$ n=12; placebo$_{IV}$/frexalimab$_{1200mg/IV}$ n=9; frexalimab$_{300mg/SC}$ n=38; frexalimab$_{1200mg/IV}$ n=39. Grey shaded area depicts the 25–75th percentiles NfL range for healthy individuals aged 40[1]. BL, baseline; DBP, double-blind period; IV, intravenous; NfL, neurofilament light chain; OLE, open-label extension; SC, subcutaneous; SD, standard deviation; W, week.
1. Vermunt L, et al. *Ann Clin Transl Neurol.* 2022;9(11):1832–1837.

- Plasma NfL levels continued to decline over 120 weeks to the range observed in healthy individuals[1]
- Overall, NfL levels decreased from baseline by 45—50% across treatment arms indicating diminished neuroaxonal damage

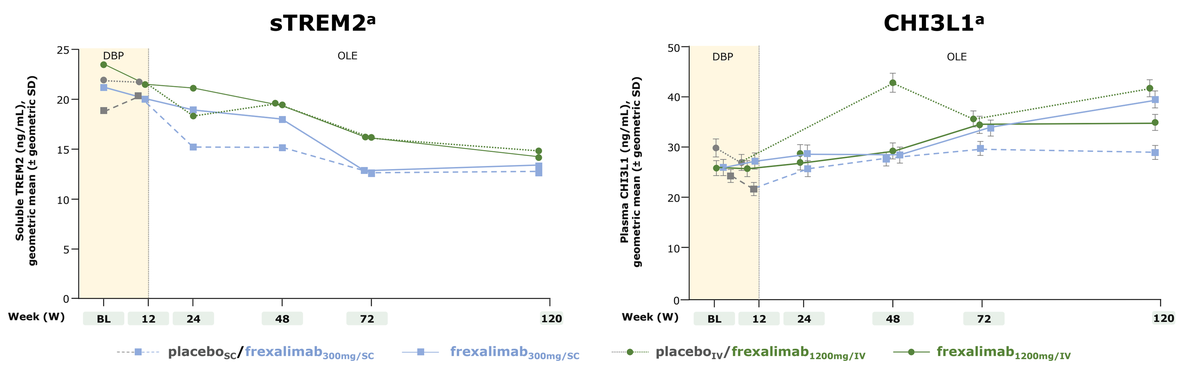
Change in plasma CXCL13 and sCD27 levels



[a]Participants per group at W120 for CXCL13 and sCD27 analyses, respectively: placebo$_{SC}$/frexalimab$_{300mg/SC}$ n=13, 13; placeboIV/frexalimab$_{1200mg/IV}$ n=9, 8; frexalimab$_{300mg/SC}$ n=40, 40; frexalimab$_{1200mg/IV}$ n=41, 40.
BL, baseline, DBP, double-bind period; CXCL13, chemokine (C-X-C motif) ligand 13; IV, intravenous; OLE, open-label extension; sCD27, soluble cluster of differentiation 27; SC, subcutaneous; SD, standard deviation; W, week.
1. Krumbholz M, et al. *Brain.* 2006;129(Pt 1):200–211; 2. DiSano KD, et al. *Mult Scler J Exp Transl Clin.* 2020;6(4):2055217320981396; 3. Cencioni MT, et al. *Front Immunol.* 2024;15:1505829.

- Plasma levels of CXCL13, an MS-implicated B-cell chemoattractant1,2, were reduced by 37—62%
- In addition, plasma levels of sCD27, primarily released by activated T cells3, declined by 16—27%
- These findings suggest that frexalimab reduces T and B cell mediated inflammatory activity

Change in plasma TREM2 and CHI3L1 levels



[a]Participants per group at W120 for sTREM2 and CHI3L1 analyses, respectively: placebo$_{SC}$/frexalimab$_{300mg/SC}$ n=13, 13; placeboIV/frexalimab$_{1200mg/IV}$ n=9, 9; frexalimab$_{300mg/SC}$ n=40, 39; frexalimab$_{1200mg/IV}$ n=41, 41.
BL, baseline, CHI3L1, chitinase-3-like protein 1; DBP, double-bind period; IV, intravenous; MS, multiple sclerosis; OLE, open-label extension; sTREM2, soluble triggering receptor expressed on myeloid cells; SC, subcutaneous;
SD, standard deviation; W, week.
1. Öhrfelt A, et al. *Mult Scler.* 2016;22(12):1587–1595; 2. Floro S, et al. *Neurol Neuroimmunol Neuroinflamm*. 2022;9(4):e1164.

- Frexalimab reduced plasma levels of sTREM2, which is shed by activated macrophages/microglia and elevated in people with MS[1], by 32—39%
- In contrast, plasma levels of CHI3L1, expressed by macrophages in the blood and glia in the brain[2], were increased by frexalimab treatment (20—52% from baseline)
- These findings demonstrate that frexalimab modulates activity of the innate immune cells

CONCLUSIONS

Plasma **NfL** levels continued to decline over 120 weeks with frexalimab treatment, with up to 50% reduction from baseline, indicating a marked **reduction in neuroaxonal damage** in people with relapsing MS

Levels of immune cell biomarkers **CXCL13** and **CD27**, associated with B-cell recruitment[1], T-cell activation[2], and MS disease activity[3], continued to decline through 120 weeks in frexalimab-treated participants, indicating sustained **suppression of inflammation** and **adaptive immunity**

Soluble **TREM2**, secreted by myeloid cells and CNS-resident microglia/macrophages[4,5], declined across frexalimab arms, indicating **reduced innate immune activity**

These results support the emerging understanding of frexalimab MoA targeting crosstalk between adaptive (T- and B-cells) and innate (macrophages/microglia) immune networks.
By modulating the activity of these networks, frexalimab may mitigate both acute and chronic neuroinflammation in MS.

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