Safety and Efficacy of Frexalimab in the Treatment of Relapsing Multiple Sclerosis: 18-month Results from the Phase 2 Open-Label Extension

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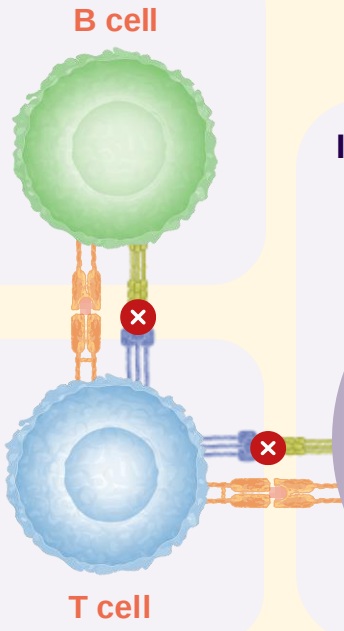
Frexalimab Inhibits the Costimulatory CD40/CD40L Pathway

Frexalimab: Proposed mechanism of action in MS

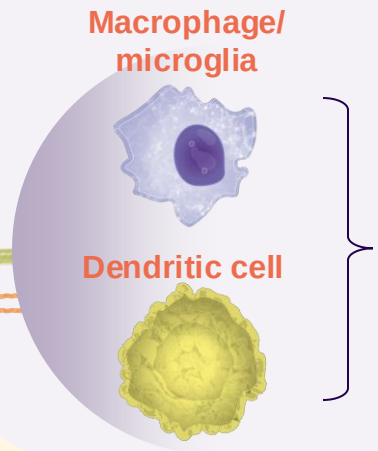
B Cells
- Activation
- Proliferation
- Antigen presentation
- Antibody production

T Cells
- Activation
- Th cell differentiation (Th1, Th17)
- Inflammatory cytokines



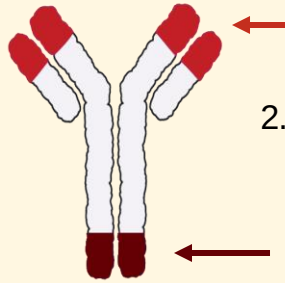
Endothelial cells
- BBB permeability

Innate immune cells

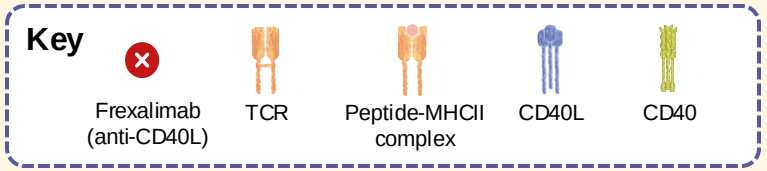


- Activation
- Inflammatory cytokines
- Antigen presentation

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



- The costimulatory CD40/CD40L pathway regulates adaptive and innate immune responses and is implicated in the pathogenesis of MS[1-8]
- By inhibiting the CD40/CD40L pathway, frexalimab may modify T and B cell activation and innate immune (macrophage/ microglia and dendritic cell) cell function, without depleting lymphocytes[9]

1.Gerritse K, et al. *Proc Natl Acad Sci USA*. 1996;93(6):2499-2504; 2. Elgueta R, et al. *Immunol Rev.* 2009;229:152-72; 3. Karnell JL, et al. *Adv Drug Deliv Rev.* 2019;141:92-103; 4. t'Hart BA, *J Neuroimmunol.* 2005;163(1-2):31-39; 5. Howard LM, et al. *J Clin Invest*. 1999;103(2):281-90; 6. Laman JD, et al. *Mult Scler.* 1998;4(3):147-53; 7. Mathur RK, et al. *Trends Parasitol.* 2006;22(3):117–22; 8. Fadul CE, Mao-Draayer Y, et al. *Neurol Neuroimmunol Neuroinflamm.* 2021;8(6):e1096; 9. Vermersch P, et al. *N Engl J Med.* 2024;390(7):589-600.

BBB, blood-brain barrier; CD40, cluster of differentiation 40; CD40L, CD40 ligand; FcγRIIa, Fc gamma receptor IIa; IgG, immunoglobulin G; MHC, major histocompatibility complex; MS, multiple sclerosis; TCR, T-cell receptor; Th, T helper.

Frexalimab Met the Primary Endpoint at Week 12 in the 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]

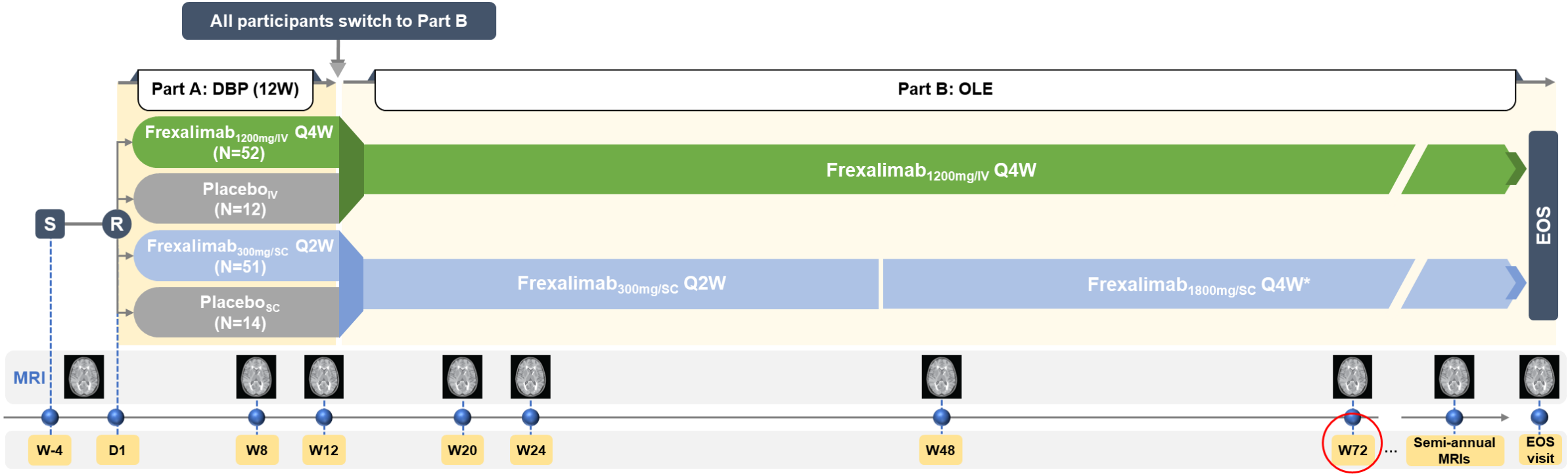
89% reduction (p = 0.0004) in **new Gd+ T1 lesions** (primary endpoint) in the 1200-mg intravenous Q4W arm vs pooled placebo at Week 12[1]

Sustained reduction in number of lesions was noted **over 48 weeks** of treatment with frexalimab[2]

Objective: To report safety and efficacy of frexalimab at 18 months (Week 72) in the OLE of the Phase 2 trial

1. Vermersch P, et al. *N Engl J Med.* 2024;390(7):589-600; 2. Giovannoni G, et al. *Neurology.* 2024;102(17_supplement_1):3284.
DBP, double-blind period; Gd+, gadolinium-enhancing; IV, intravenous; MS, multiple sclerosis; OLE, open-label extension; Q4W, every 4 weeks.

Trial Design and Outcomes



Trial Outcomes

- *Safety*: Adverse event incidence
- *MRI outcomes*[**]: Number of Gd+ T1 lesions, number of new or enlarging T2 lesions, and change in T2 lesion volume
- *Clinical outcomes*: Annualized relapse rate, EDSS score
- *Blood-based biomarkers*: Lymphocyte count and immunoglobulin (IgG and IgM) levels

[*]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. The high SC dose was administered via syringe infusion material upon its availability on site and local approval of amended protocol. The first 1800 mg Q4W SC dose was administered on 21 Aug 2023 and 7 of 57 participants in the SC arm had their W72 MRI assessments after receiving the high-dose frexalimab.

[**]For all MRI-derived endpoints, a blinded review was performed at a central facility (NeuroRx).

D, day; DBP, double-blind period; EDSS, Expanded Disability Status Scale; EOS, end of study; Gd+, gadolinium-enhancing; Ig, immunoglobulin; IV, intravenous; MRI, magnetic resonance imaging; N, number of participants; OLE, open-label extension; Q2W, every 2 weeks; Q4W, every 4 weeks; R, randomization; S, screening; SC, subcutaneous; W, week.

Participant Disposition and Baseline Characteristics

At baseline:[1]

- Mean (SD) age **36.6 (9.4) years**
- **66% women**
- MS type: **94% RRMS**, 6% SPMS with relapses

129 randomized participants

DBP (Part A)

125 (97%) completed Part A and entered Part B

OLE (Part B)

14 (11%) participants discontinued

- **Participant's decision to withdraw (n=7)**
  - n=3, frexalimab$_{1200mg/IV}$
  - n=3*, frexalimab$_{300mg/SC}$
  - n=1, placebo$_{SC}$/frexalimab$_{300mg/SC}$
- **Emergency situation due to the Ukraine war (n=3)**
  - n=1, frexalimab$_{1200mg/IV}$
  - n=1, frexalimab$_{300mg/SC}$
  - n=1, placebo$_{IV}$/frexalimab$_{1200mg/IV}$
- **AEs** (n=3)**
  - COVID-19: n=1, placebo$_{IV}$/frexalimab$_{1200mg/IV}$
  - Papillary thyroid cancer: n=1, frexalimab$_{1200mg/IV}$
  - ALT increased: n=1¥, frexalimab$_{1200mg/IV}$
- **HCP decision: n=1**, frexalimab$_{300mg/SC}$

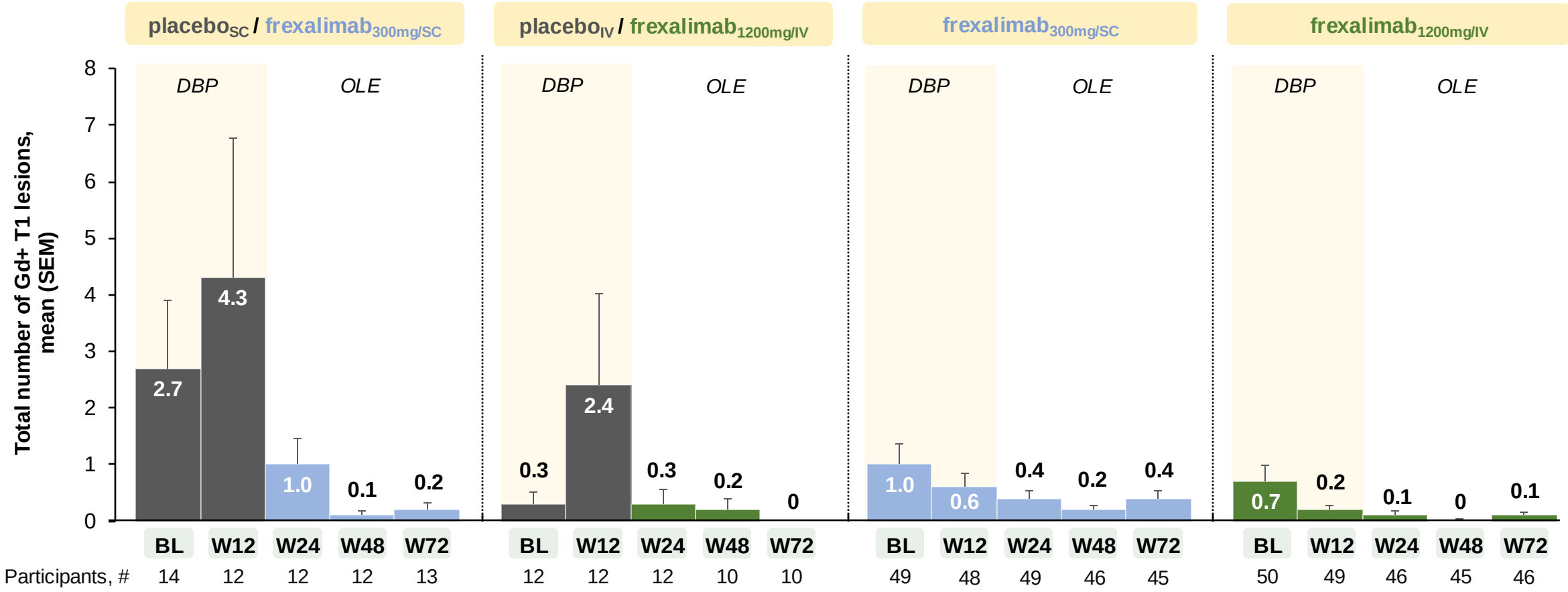
111 (86%) participants completed Week 72 and had ongoing treatment as of 2 Feb 2024 (median [range] follow-up duration 104 [80–132] weeks)

*One participant withdrew as she intended to become pregnant.
**Discontinuations due to protocol-defined AEs.
¥Recurring, isolated ALT level increases, the first of which occurred at 6 months after starting treatment (9x ULN) 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.

1. Vermersch P, et al. *N Engl J Med.* 2024;390(7):589-600.

AE, adverse event; ALT, alanine aminotransferase; COVID-19, coronavirus disease 2019; DBP, double-blind period; HCP, healthcare professional; IV, intravenous; MS, multiple sclerosis; OLE, open-label extension; RRMS, relapsing-remitting MS; SC, subcutaneous; SD, standard deviation; SPMS, secondary progressive MS; ULN, upper limit of normal.

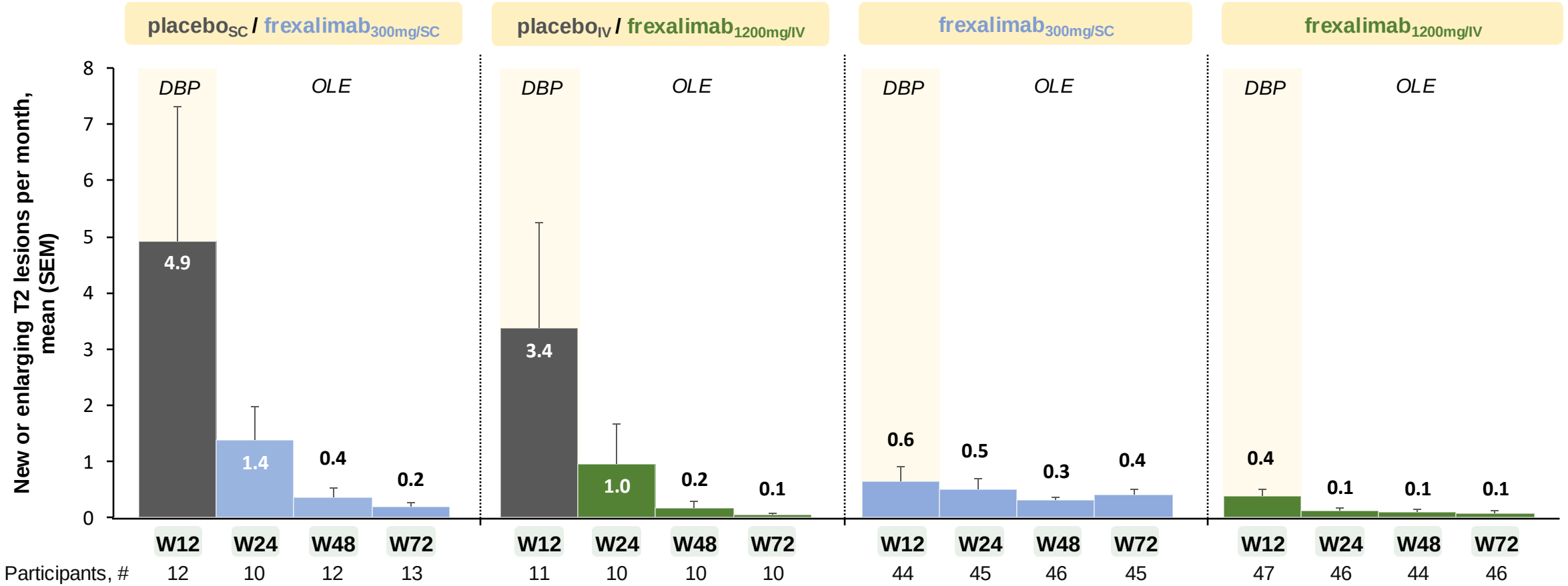
Total Number of Gd+ T1 Lesions



- Gd+ T1 lesions remained low at Week 72 in participants who switched from placebo to frexalimab at Week 12 and in those who continued receiving frexalimab after Week 12

BL, baseline; Gd+, gadolinium-enhancing; IV, intravenous; OLE, open-label extension; SC, subcutaneous; SEM, standard error of the mean; W, week.

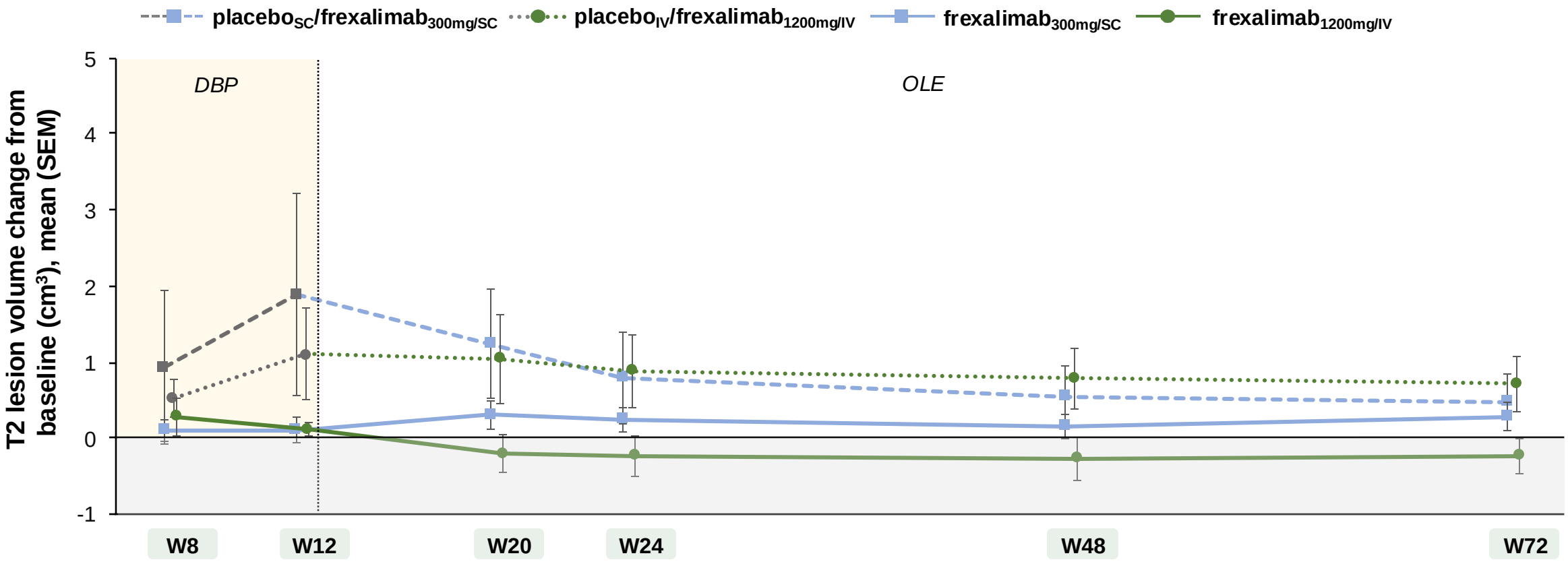
New or Enlarging T2 Lesions Monthly Count



- New or enlarging T2 lesions monthly count* remained low through Week 72 in participants who switched from placebo to frexalimab at Week 12 and in those who continued receiving frexalimab after Week 12

*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; SC, subcutaneous; SEM, standard error of the mean; W, week.

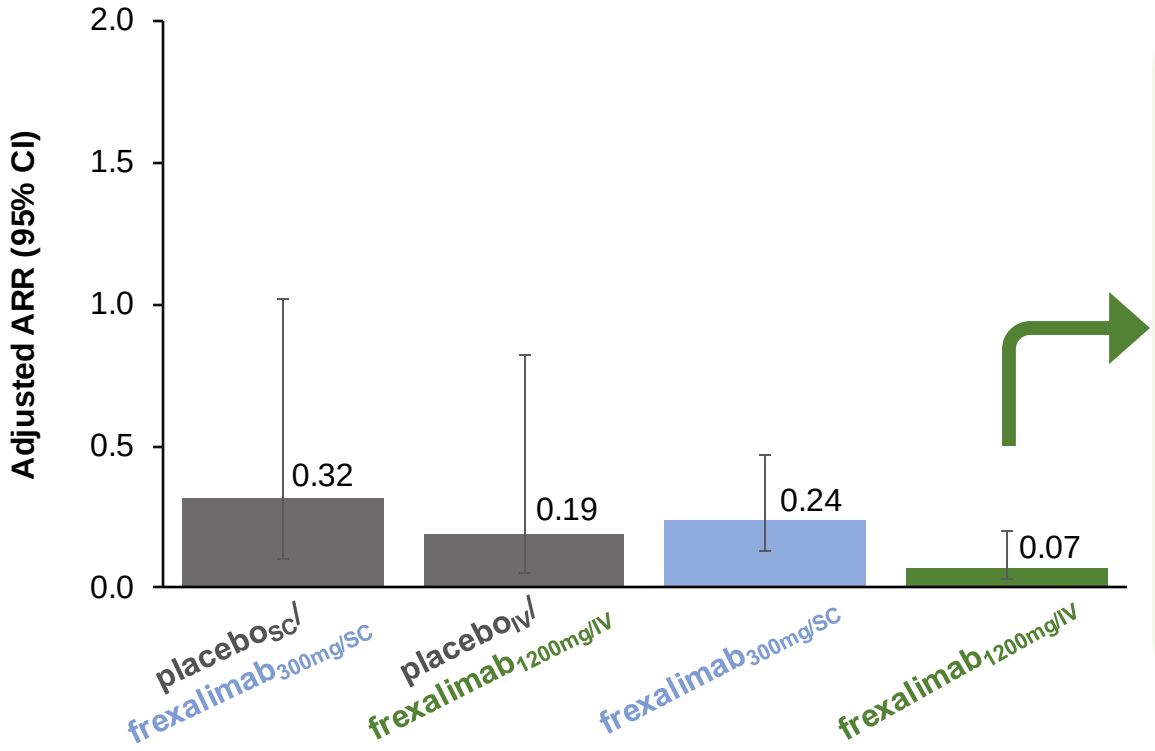
T2 Lesion Volume Change From Baseline

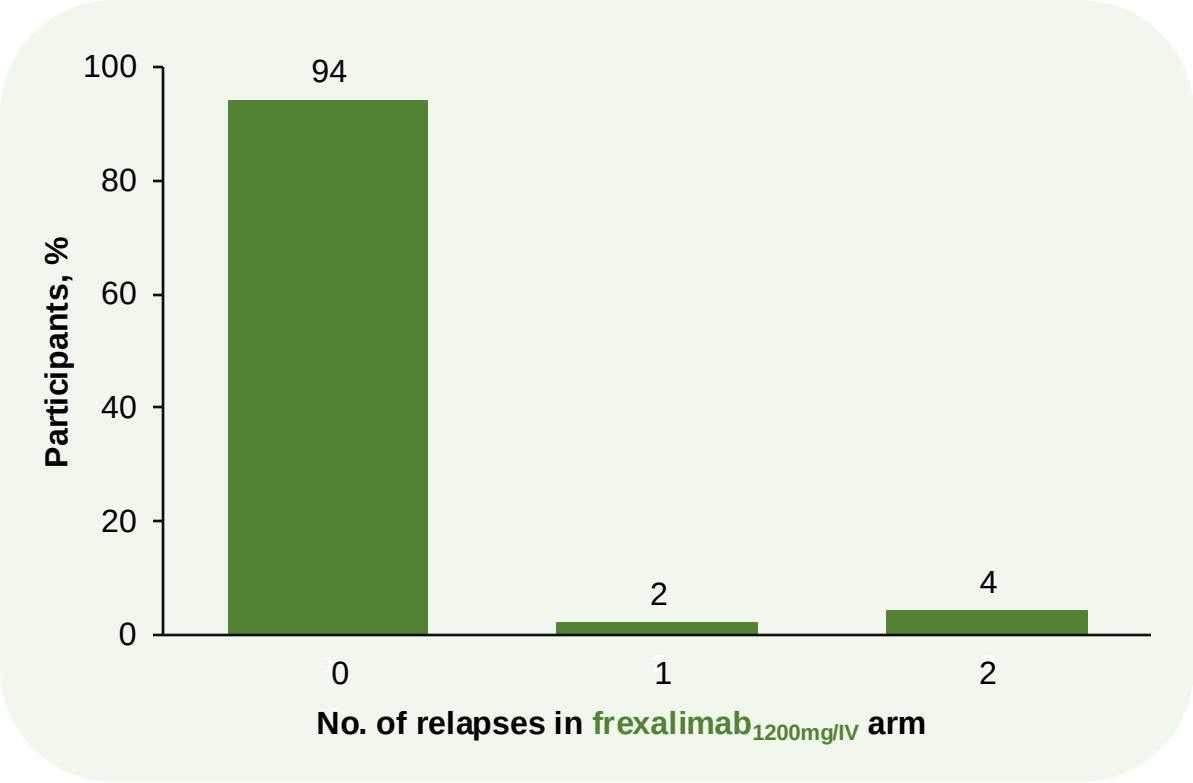


- Change in T2 lesion volume from baseline remained low through Week 72 in participants who switched from placebo to frexalimab at Week 12 and in those who continued receiving frexalimab after Week 12

DBP, double-blind period; IV, intravenous; OLE, open-label extension; SC, subcutaneous; SEM, standard error of the mean; W, week.

Frequency of Confirmed Clinical Relapses From Baseline to Week 72

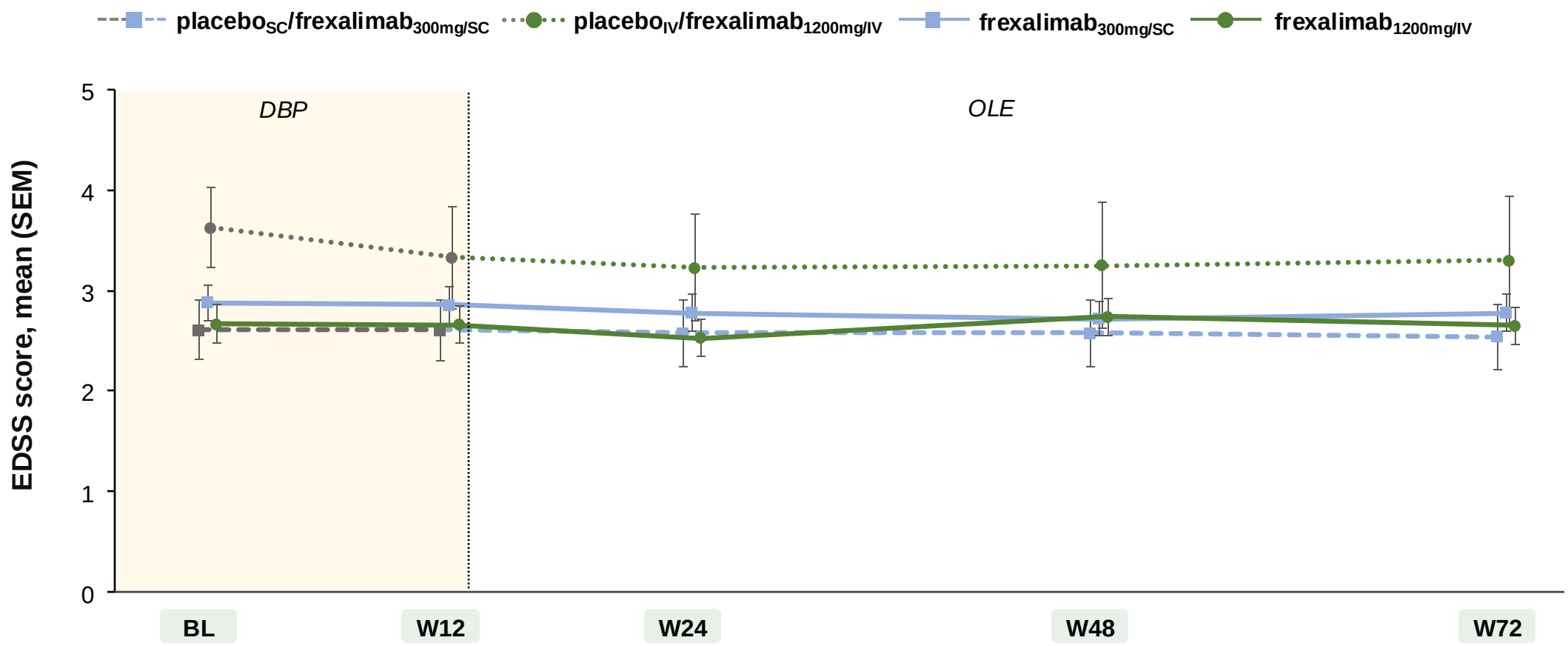




- Adjusted ARR* for participants originally assigned to frexalimab$_{1200mg/IV}$ was low (0.07 [95% CI, 0.03 – 0.20])
  - 94% of OLE participants in frexalimab$_{1200mg/IV}$ arm remained relapse-free from baseline up to their Week 72 visit

*Estimated using a negative binomial regression model including the total number of confirmed relapses (as per the protocol) with onset over considered period (baseline – week 72 visit date) as response variable and initial treatment as covariate, with log transformed standardized period duration included as an offset variable.
ARR, annualized relapse rate; CI, confidence interval; IV, intravenous; OLE, open-label extension; SC, subcutaneous.

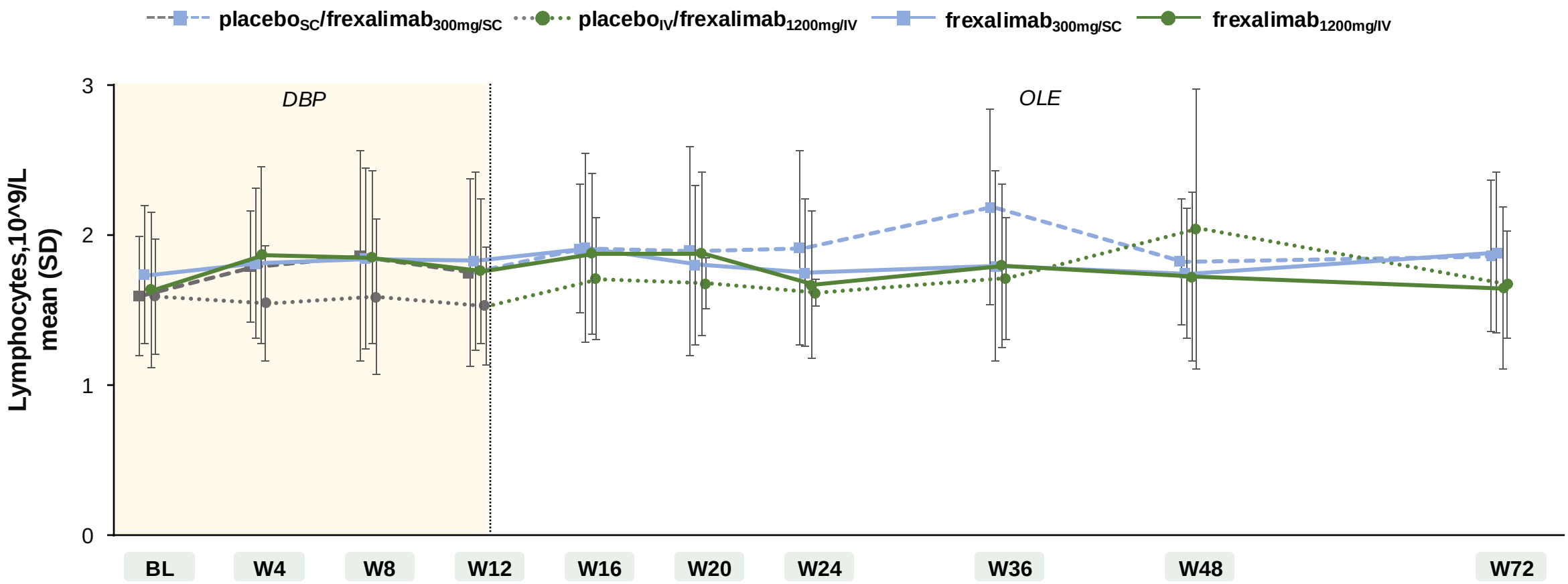
EDSS Score



Mean EDSS scores remained low and stable through Week 72

A higher EDSS score represents a higher level of disability.
BL, baseline; DBP, double-blind period; EDSS, Expanded Disability Status Scale; IV, intravenous; OLE, open-label extension; SC, subcutaneous; SEM, standard error of the mean; W, week.

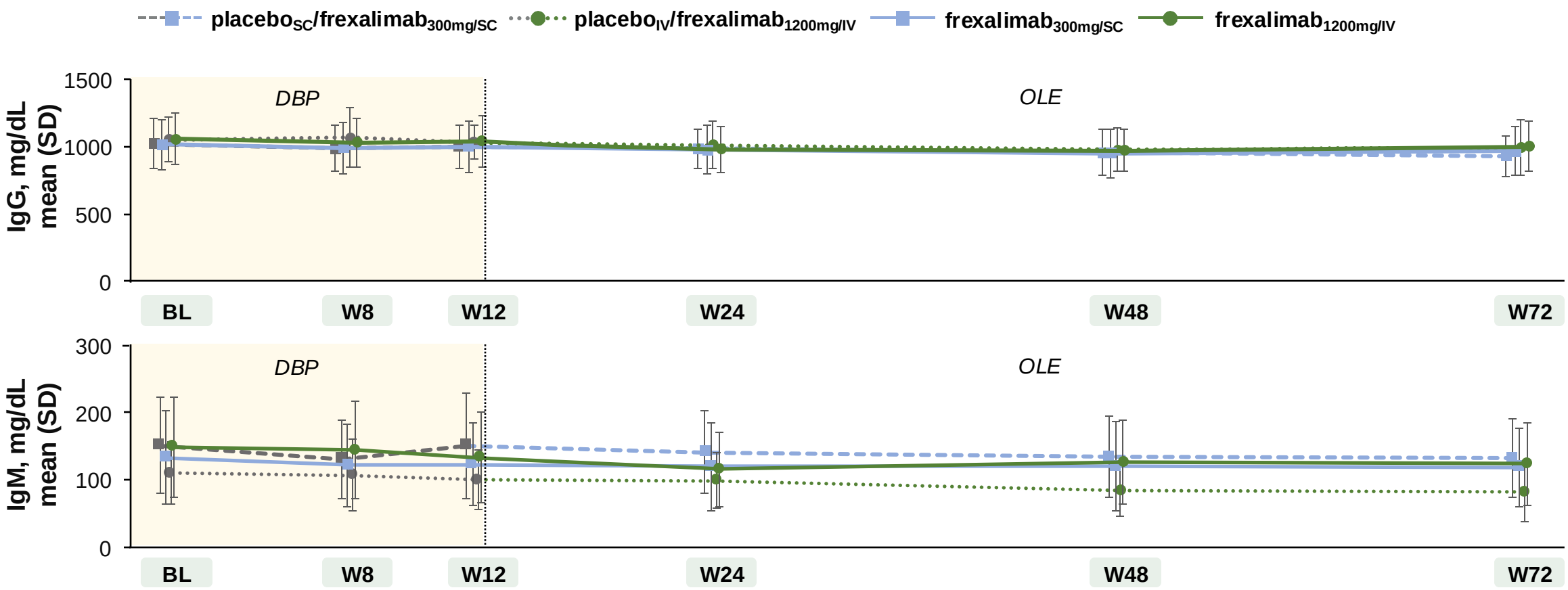
Lymphocyte Counts



Lymphocyte counts remained stable over 72 weeks

BL, baseline; DBP, double-blind period; IV, intravenous; OLE, open-label extension; SC, subcutaneous; SD, standard deviation; W, week.

Immunoglobulin Levels



IgG and IgM levels showed stability or marginal decrease over 72 weeks

BL, baseline; DBP, double-blind period; Ig, immunoglobulin; IV, intravenous; OLE, open-label extension; SC, subcutaneous; SD, standard deviation; W, week.

Summary of AEs From Week 12 Until Cut-off at Week 72

Participants, n (%)	placebo$_{SC}$/ frexalimab$_{300mg/SC}$ (N=14)	placebo$_{IV}$/ frexalimab$_{1200mg/IV}$ (N=12)	frexalimab$_{300mg/SC}$ (N=49)	frexalimab$_{1200mg/IV}$ (N=50)
Any AE	11 (79)	8 (67)	41 (84)	33 (66)
Serious AEs	0	0	2 (4)[*]	4 (8)[¥]
AEs leading to death	0	0	0	0
AEs leading to permanent treatment discontinuation	0	1 (8)[¶]	0	2 (4)[‡]
Most Common AEs (Occurring in ≥10% in any arm)[**]				
Nasopharyngitis	3 (21)	1 (8)	5 (10)	7 (14)
COVID-19[§]	3 (21)	1 (8)[¶]	5 (10)	6 (12)
Headache	0	1 (8)	8 (16)	5 (10)

[*]In the frexalimab$_{300mg/SC}$ arm, serious AEs of pneumonia and road traffic accident (n=1 each) were reported.
[¥]In the frexalimab$_{1200mg/IV}$ arm, serious AEs of Escherichia pyelonephritis, gallbladder enlargement, lower limb fracture, and papillary thyroid cancer (n=1 each) were reported, of which AE of papillary thyroid cancer[‡] led to permanent treatment discontinuation.
[§] All COVID-19 (n=15) cases were of mild to moderate intensity, of which one COVID-19 event in the placebo$_{IV}$/frexalimab$_{1200mg/IV}$ arm[¶] led to permanent treatment discontinuation.
[**]Dosing greater than protocol-defined threshold (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) was reported using AE process; 18 such events are not included in this table.
AE, adverse event; COVID-19, coronavirus disease 2019; IV, intravenous; SC, subcutaneous.

Adverse Events of Special Interest

Participants, n (%)	placebo$_{SC}$/ frexalimab$_{300mg/SC}$ (N=14)	placebo$_{IV}$/ frexalimab$_{1200mg/IV}$ (N=12)	frexalimab$_{300mg/SC}$ (N=49)	frexalimab$_{1200mg/IV}$ (N=50)
AEs of special interest	4 (29)	1 (8)	7 (14)	9 (18)
COVID-19*	3 (21)	1 (8)	5 (10)	6 (12)
ALT increased	0	0	0	2 (4)¥
Escherichia pyelonephritis	0	0	0	1 (2)
Pneumonia	0	0	1 (2)	0
Administration site pain	1 (7)	0	0	0
Pregnancy	0	0	1 (2)§	0

*All COVID-19 (n=15) cases were of mild to moderate intensity, of which one COVID-19 event in the placebo$_{IV}$/frexalimab$_{1200mg/IV}$ arm led to permanent treatment discontinuation.
¥During the OLE period, 2 participants in the frexalimab$_{1200mg/IV}$ 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 frexalimab$_{1200mg/IV}$ 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.
§Participant withdrew as she intended to become pregnant.
AE, adverse event; ALT, alanine aminotransferase; COVID-19, coronavirus disease 2019; IV, intravenous; OLE, open-label extension; SC, subcutaneous; ULN, upper limit of normal.

Conclusions

Frexalimab treatment continues to show a **sustained reduction of disease activity** as measured by MRI
- **Gd+ T1 lesions** and **new or enlarging T2 lesions** remained **low** through Week 72
- **T2 lesion volume** remained **stable** during the OLE up to Week 72

Clinical endpoints remained stable during the OLE up to Week 72
- **ARR** in the frexalimab$_{1200mg/IV}$ arm was **low** (0.07 [95% CI, 0.03–0.20]); **94%** participants were **relapse-free**
- **EDSS score** was stable from baseline to Week 72

Frexalimab remained **well-tolerated** with no emergence of new safety signals
- **Lymphocyte counts** were stable over 72 weeks

These sustained efficacy and safety data strengthen the rationale for targeting CD40L in MS and support further development of frexalimab in Phase 3 MS trials as a potential high-efficacy, non-lymphocyte-depleting therapy

Efficacy and safety of frexalimab is currently being investigated in two actively recruiting Phase 3 trials:

FREXALT CLINICAL TRIAL
NCT06141473
Relapsing MS

FREVIVA CLINICAL TRIAL
NCT06141486
Non-relapsing secondary progressive MS