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Durable Impact of Immune Cell Reconstitution Over 4 Years Following Short Course Cladribine Tablets: Results From MAGNIFY-MS Extension Study

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RESEARCH IN CONTEXT

1. **The patterns of immune cell depletion and repopulation confirm the durable effect of short-course treatment with CladT in Years 1 and 2, lasting through treatment-free Years 3 and 4.**
2. **Changes in immune cells and serum proteins reported in parallel with efficacy and safety outcomes help with our understanding of CladT being convenient, safe, and efficacious treatment option in participants with highly active relapsing MS.**

OBJECTIVES

To describe blood biomarker dynamics (immune cell subsets, serum immunoglobulins [Ig] and serum neurofilament light chain [NfL]) up to 4 years from initiating treatment with cladribine tablets (CladT).

INTRODUCTION

MAGNIFY-MS Extension (NCT04783935) was a 2-year, treatment-free, follow-up study to the parent 2-year phase IV study **MAGNIFY-MS** (NCT03364036).

Blood biomarkers were analyzed to assess the long-term effect of CladT on disease activity, particularly during the treatment-free period in Years 3 and 4.

METHODS

- Participants with highly active relapsing multiple sclerosis (MS) who had completed two short-course treatments with CladT (3.5 mg/kg cumulative dose over 2 years) in **MAGNIFY-MS** were eligible to enter this **Extension** study, forming a cumulative observational period of 4 years.
- Peripheral blood mononuclear cells were collected at the indicated time points. Panels of B, T, and natural killer (NK) cells were analyzed using surface cell markers as described previously.[1,2]
- Serum IgG and IgM levels were analyzed by nephelometric assay, and serum NfL levels were analyzed using Quanterix NF-light chain assay at the indicated time points.[3]
- Absolute cell counts (and serum Ig/NfL levels) and the median percentage change from baseline (BL) were assessed; all analyses were descriptive.

RESULTS

- The **MAGNIFY-MS Extension** study included 219 participants of mean age (± standard deviation) 40.4 (9.45) years; 64.8% were female (**Supplementary Table 1**).
- The median percentage change from BL for selected B cells and T cells are shown in **Figures 1 and 2**, respectively, with additional B cell and T cell subsets and NK cells shown in **Supplementary Figures 1–3**. The absolute cell counts for B, T, and NK cells are shown in **Supplementary Figures 4–6**.

SCAN FOR INTERACTIVE GRAPHS

Figure 1. Sustained Reduction Below BL of Memory B Cells and Repopulation of Naïve B Cells

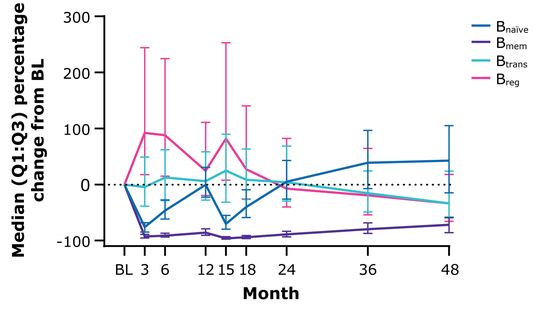


Figure 2. Sustained Reduction Below BL of T Cells Over 4 Years

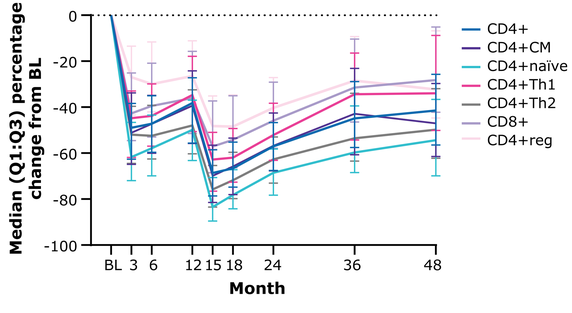


Figure 3. Serum IgG and IgM Remained Within Normal Limits

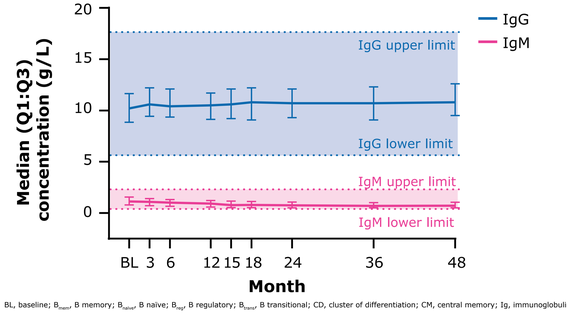
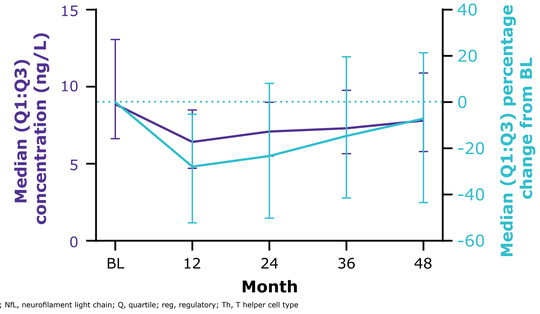


Figure 4. Serum NfL Concentration Remained Below BL Over 4 Years



BL, baseline; B_{mem}, B memory; $B_{naïve}$, B naïve; B_{reg}, B regulatory; B_{trans}, B transitional; CD, cluster of differentiation; CM, central memory; Ig, immunoglobulin; NfL, neurofilament light chain; Q, quartile; reg, regulatory; Th, T helper cell type

- Memory B cells showed a significant and sustained reduction (nadir at M15, -96.2%) to month (M) 48. Naïve B cells were reduced on CladT treatment (nadir at M3, -76.1%) and then showed a continual repopulation over time. Transitional and regulatory B cells were reduced below BL from M24 to M48 (**Figure 1**).
- T cells reached nadir at M15 (M18 for CD4+ regulatory) and then showed a gradual recovery through to M48 (**Figure 2**).
- NKp46 cells reached nadir at M6, then increased above BL to M48. $CD16^{low}CD56^{bright}$ cells reached nadir at M3, then increased above BL to M24 before reducing through M24 to M48 (**Supplementary Figure 3**).
- IgG and IgM levels remained within normal limits for most participants (**Figure 3**).
- Serum NfL concentration was reduced after first treatment course and remained low during the observation period (**Figure 4**).
- These immunophenotypic changes are supported by previously reported clinical data and are reflective of the disease control achieved with CladT:
  - The annualized relapse rate (ARR) remained low at 0.09 over the 4-year study period (**Supplementary Figure 7**).[4]
  - A decrease in T1 gadolinium-enhancing lesion counts and annualized active T2 lesions was observed at M48 compared to BL period (**Supplementary Figure 8**).[4]
- No increase in infection rate was observed during the study despite the global COVID-19 pandemic (**Supplementary Table 2**).

CONCLUSIONS

- **The multifaceted changes in the immune response over 4 years, supported by a low ARR and a decrease in magnetic resonance imaging activity, confirm the lasting benefit of short-term CladT dosing through the treatment-free period.**
- **These data suggest effective reconstitution of the immune system towards a more homeostatic and less pathogenic state without the need for continuous immunosuppression.**

SCAN FOR AFFILIATIONS, DISCLOSURES, AND SUPPLEMENTARY MATERIALS

References: 1. Wiendl H, et al. *Neurol Neuroimmunol Neuroinflamm*. 2022;10(1):e200048. 2. Wiendl H, et al. *Front Immunol*. 2025;16:1512189. 3. Quanterix Simoa HD-1 Analyzer (Labcorp/Monogram, 345 Oyster Point Blvd, South San Francisco, CA 94080, USA). 4. De Stefano N, et al. The 40th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), September 18–20, 2024, Copenhagen, Denmark: Poster #349.

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Supplementary Materials

Supplementary Table 1.[1] Participant Characteristics at Entry to MAGNIFY-MS Extension

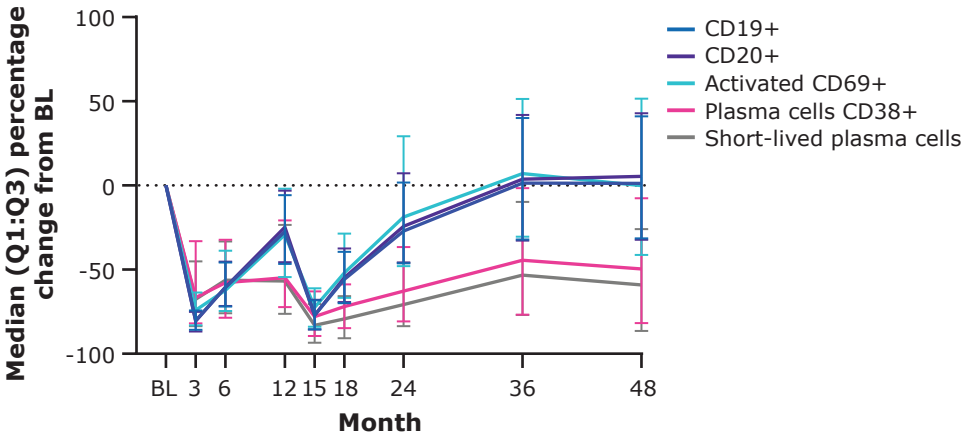
	MAGNIFY-MS Extension (N=219)
Female, n (%)[a]	142 (64.8)
Age at informed consent, years, mean ± SD[b]	40.4 ± 9.45
Age ≤40 years at informed consent, n (%)[b]	102 (46.6)
Time since onset of MS, months, median (IQR)[a]	53.82 (16.39, 125.34)
Number of relapses within 12 months prior to baseline, n (%)[a]	
0	2 (0.9)
1	91 (41.6)
2	103 (47.0)
>2	23 (10.5)
EDSS >3 at baseline, n (%)[a]	51 (23.3)
Number of previous DMTs, n (%)[a]	
0	89 (40.6)
1	76 (34.7)
2	40 (18.3)
>2	14 (6.4)
Presence of any T1 Gd+ lesions, n (%)[c]	110 (50.2)
Presence of any active T2 lesions, n (%)[c]	94 (42.9)
Non-evaluable	2 (0.9)

[a]Data recorded at MAGNIFY-MS parent study baseline. [b]Informed consent for Extension study. [c]During the MAGNIFY-MS baseline period (the period between the screening and the baseline MRI scan in MAGNIFY-MS study).
DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; IQR, interquartile range; MRI, magnetic resonance imaging; MS, multiple sclerosis; SD, standard deviation

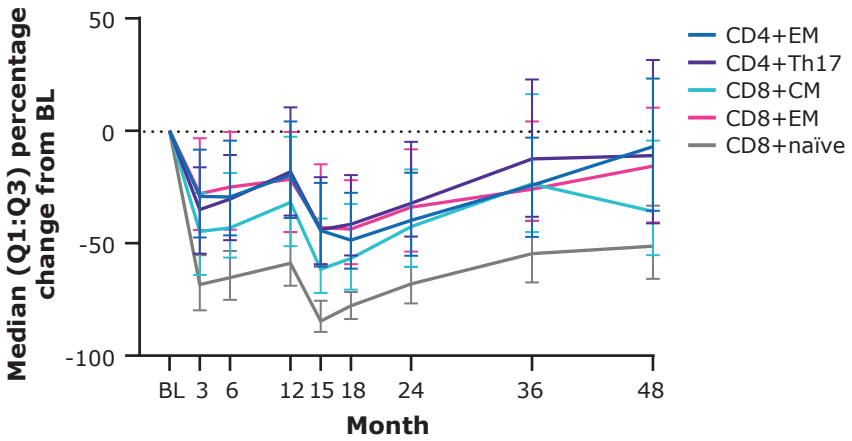
Reference: 1. This table has been previously presented at The 40th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), September 18–20, 2024, Copenhagen, Denmark (Poster #349).

Supplementary Materials

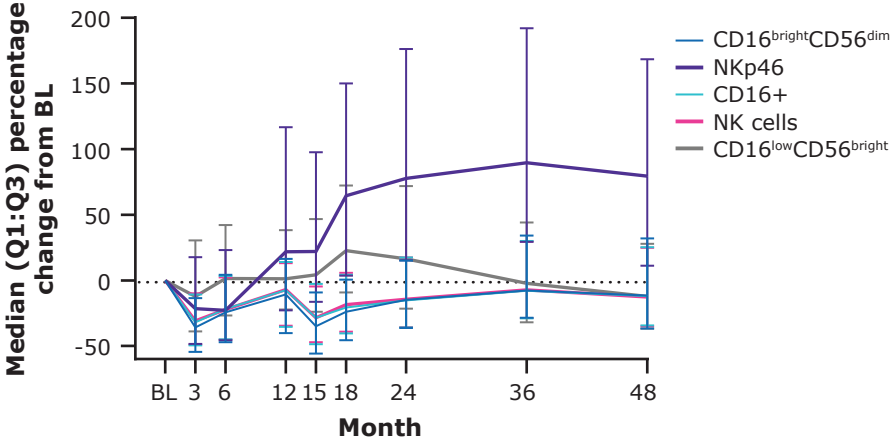
Supplementary Figure 1. Reduction Below BL in B cells; Repopulation in CD19+, CD20+, and Activated CD69+ to BL at M36–M48



Supplementary Figure 2. Sustained Reduction Below BL in T Cells Over 4 Years



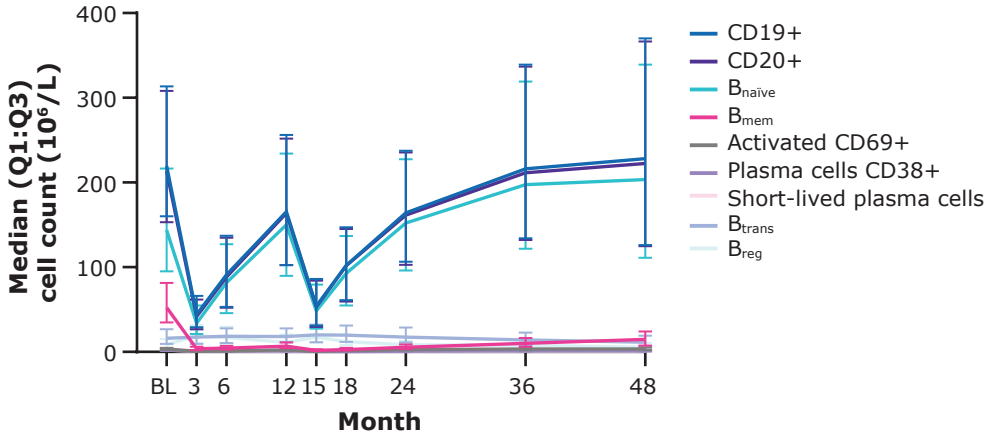
Supplementary Figure 3. Initial Reduction Below BL in NK Cells; Repopulation in NKp46 Cells; Repopulation in $CD16^{low}CD56^{bright}$ Cells Followed by Reduction



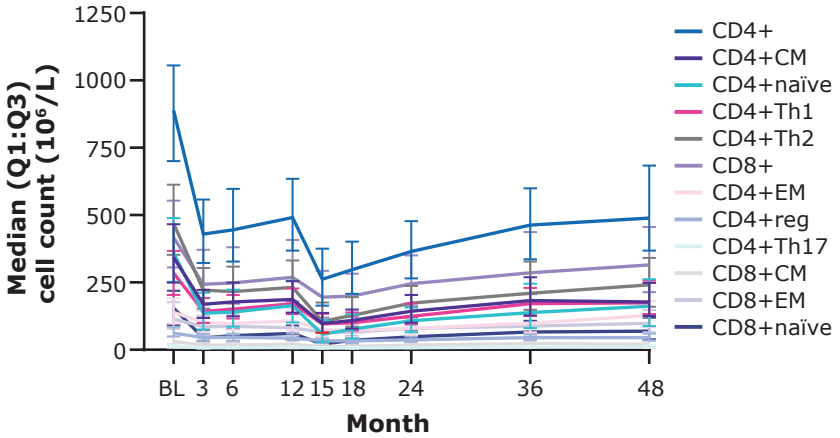
BL, baseline; CD, cluster of differentiation; CM, central memory; EM, effector memory; NK, natural killer; Q, quartile; Th, T helper cell type

Supplementary Materials

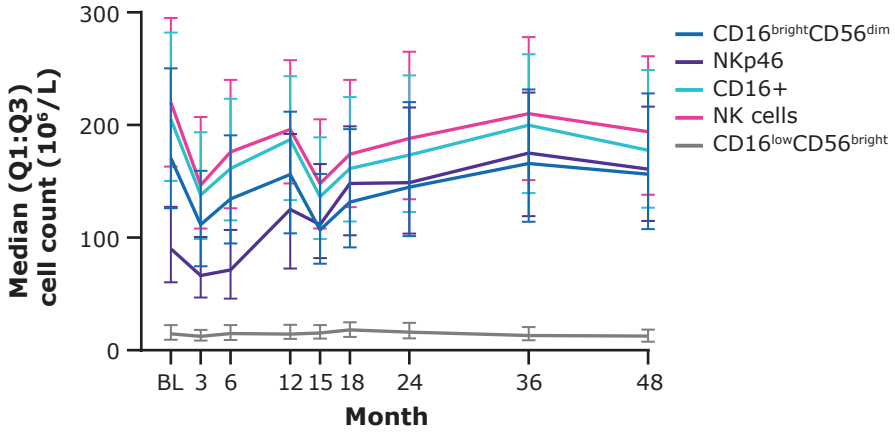
Supplementary Figure 4. Absolute Cell Count for B Cells Over 4 Years



Supplementary Figure 5. Absolute Cell Count for T Cells Over 4 Years



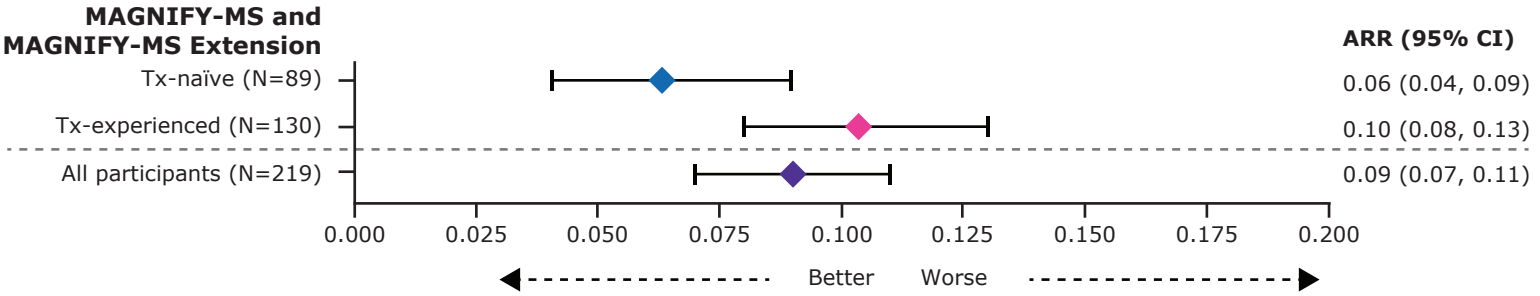
Supplementary Figure 6. Absolute Cell Count for NK Cells Over 4 Years



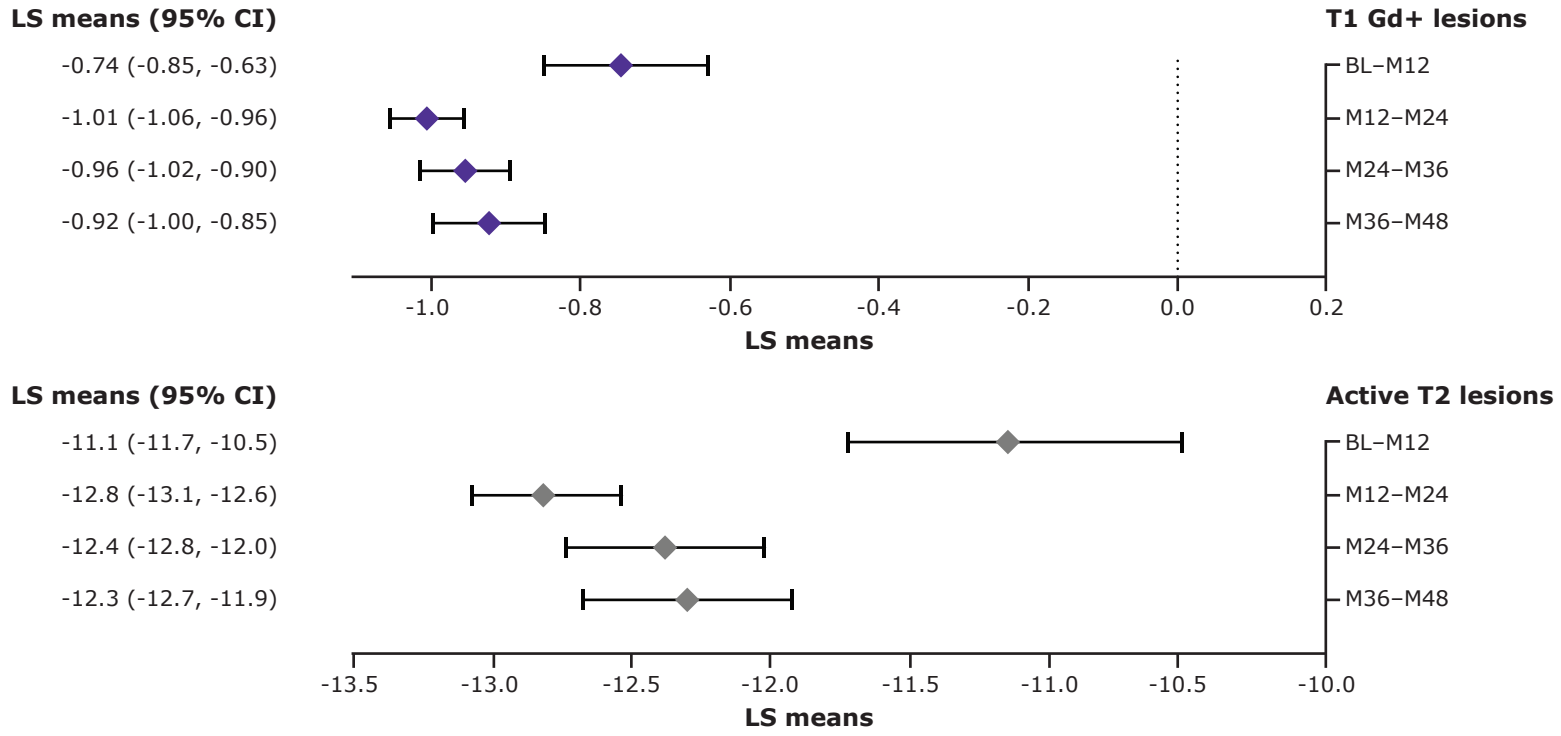
BL, baseline; B_{mem}, B memory; $B_{naïve}$, B naïve; B_{reg}, B regulatory; B_{trans}, B transitional; CD, cluster of differentiation; CM, central memory; EM, effector memory; NK, natural killer; Q, quartile; reg, regulatory; Th, T helper cell type

Supplementary Materials

Supplementary Figure 7.[1] Low ARRs Were Observed Over 4 Years, Especially For Tx-Naïve Participants



Supplementary Figure 8.[1] Marked Reductions Versus BL Period Were Observed for T1 Gd+ and Active T2 Lesions Over 4 Years



The BL period is defined as the period between the screening and BL MRI scan in the MAGNIFY-MS study.

ARR, annualized relapse rate; BL, baseline; CI, confidence interval; Gd+, gadolinium-enhancing; LS, least squares; M, month; MRI, magnetic resonance imaging; Tx, treatment

Reference: 1. This figure has been previously presented at The 40th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), September 18–20, 2024, Copenhagen, Denmark (Poster #349).

Supplementary Materials

Supplementary Table 2.[1] Overview of Adverse Events During Extension Study Period

	MAGNIFY-MS Extension (N=219), n (%)
Any AE[a]	142 (64.8)
Mild	87 (39.7)
Moderate	47 (21.5)
Severe	8 (3.7)
Any study treatment-related AE[a]	21 (9.6)
Mild	11 (5.0)
Moderate	9 (4.1)
Severe	1 (0.5)
Any serious AE	13 (5.9)
Any study treatment-related serious AE	3 (1.4)
Infections (bronchitis)	1 (0.5)
Infections (peritonsillitis)	1 (0.5)
Infections (tonsillitis)	1 (0.5)
Neoplasms (malignant melanoma)	1 (0.5)
Participants with ≥1 AE[b]	
COVID-19	50 (22.8)
Headache	16 (7.3)
Nasopharyngitis	15 (6.8)
Upper respiratory tract infection	12 (5.5)
Influenza	11 (5.0)
Back pain	9 (4.1)
Pain in extremity	8 (3.7)
Bronchitis	7 (3.2)
Nausea	6 (2.7)
Pregnancy	6 (2.7)
Lymphopenia	5 (2.3)

[a]Worst severity per participant is reported. Related AEs are events with relationship set to 'Missing', 'Unknown', or 'Yes'. AEs reported during the Extension study period. [b]Most common AEs that affect ≥6 of total participants presented. Lymphopenia displayed as AE of interest.
AE, adverse event; COVID-19, coronavirus disease 2019

Reference: 1. This table has been previously presented at The 40th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), September 18–20, 2024, Copenhagen, Denmark (Poster #349).

Supplementary Materials

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Disclosures

HW is a member of scientific advisory boards/steering committees for Bayer, Biogen, the healthcare business of Merck KGaA, Darmstadt, Germany, Novartis, Roche, Sanofi, and Teva. He received speaker honoraria and travel support from Bayer, Biogen, CSL Behring, EMD Serono, Fresenius Medical Care, the healthcare business of Merck KGaA, Darmstadt, Germany, Omniamed, Novartis, Sanofi, and Teva. He received compensation as a consultant from Biogen, the healthcare business of Merck KGaA, Darmstadt, Germany, Novartis, Omniamed, Roche, and Sanofi. He has received research support from Bayer, Biogen, the healthcare business of Merck KGaA, Darmstadt, Germany, Novartis, Sanofi, and Teva, as well as the German Ministry for Education and Research (BMBF), German Research Foundation (DFG), Else Kröner Fresenius Foundation, Fresenius Foundation, Hertie Foundation, NRW Ministry of Education and Research, Interdisciplinary Center for Clinical Studies (IZKF) Muenster, and RE Children's Foundation.

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XM has received compensation for lecture honoraria and travel expenses, participation in scientific meetings, clinical trial steering committee membership, or clinical advisory board participation in recent years from Abbvie, Actelion, Alexion, Bial PD, Biogen, Bristol-Myers Squibb/Celgene, EMD Serono, Genzyme, Hoffmann-La Roche, Immunic Therapeutics, Janssen Pharmaceuticals, Medday, Medscape, the healthcare business of Merck KGaA, Darmstadt, Germany, Mylan, Nervgen, Neuraxpharm, Novartis, Peervoice, Samsung-Biosys, Sandoz, Sanofi-Genzyme, Teva Pharmaceutical, TG Therapeutics, Excemed, ECTRIMS, MSIF, and NMSS or any of their affiliates.

AA has received over the last 5 years honoraria or consulting fees for participating in advisory boards related to clinical trials design, trial steering committees, and data and safety monitoring committees from Biogen, Bristol Myers Squibb, Novartis, the healthcare business of Merck KGaA, Darmstadt, Germany, Roche, and Sanofi; and research support for investigator-initiated trials and MS patients' benefits activities from Bristol Myers Squibb, Biogen, the healthcare business of Merck KGaA, Darmstadt, Germany, Novartis, Roche, and Sanofi.

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AP has received speaking honoraria and travel expenses for participation in scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past years, and/or received operating grants from Alexion, Bayer, Biogen, Celgene (Bristol Myers Squibb), EMD Serono, Novartis, Roche, Sanofi, and Teva.

LL has received honoraria for consulting services or speaking activities from Bristol-Myers Squibb, Janssen-Cilag, the healthcare business of Merck KGaA, Darmstadt, Germany, Novartis, and Roche; and research support from the healthcare business of Merck KGaA, Darmstadt, Germany, and Novartis.

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FS has served on scientific advisory boards, been on the steering committees of clinical trials, served as a consultant, received support for congress participation, received speaker honoraria, or received research support for his laboratory from Biogen, Celgene (Bristol Myers Squibb), EMD Serono, the healthcare business of Merck KGaA, Darmstadt, Germany, Novartis, Roche, Sanofi, and Teva.

CP and **AN** are employees of the healthcare business of Merck KGaA, Darmstadt, Germany.

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LG is an employee of EMD Serono, Billerica, MA, USA.

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