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Long-Term Effectiveness of Cladribine Tablets Over 4 Years in Relapsing Multiple Sclerosis: Results From the MAGNIFY-MS Extension Study

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RESEARCH IN CONTEXT

1. **The high NEDA-3 rate and low ARR findings from MAGNIFY-MS Extension over 4 years after initial dosing support the early use of short-course cladribine tablets treatment for Tx-naïve people with MS.**
2. **Overall, the findings are consistent with results of Phase III clinical studies and real-world observations, [1, 2] where the magnitude of the clinical benefit over the short 2-year treatment course was maintained in Years 3 and 4.**

OBJECTIVES

To report 4-year efficacy and safety data from the MAGNIFY-MS Extension study.

INTRODUCTION

MAGNIFY-MS (NCT03364036) was a 2-year, phase IV study, which demonstrated the rapid onset of action, efficacy and safety of cladribine tablets treatment in participants (n=270) with highly active relapsing multiple sclerosis. [3]

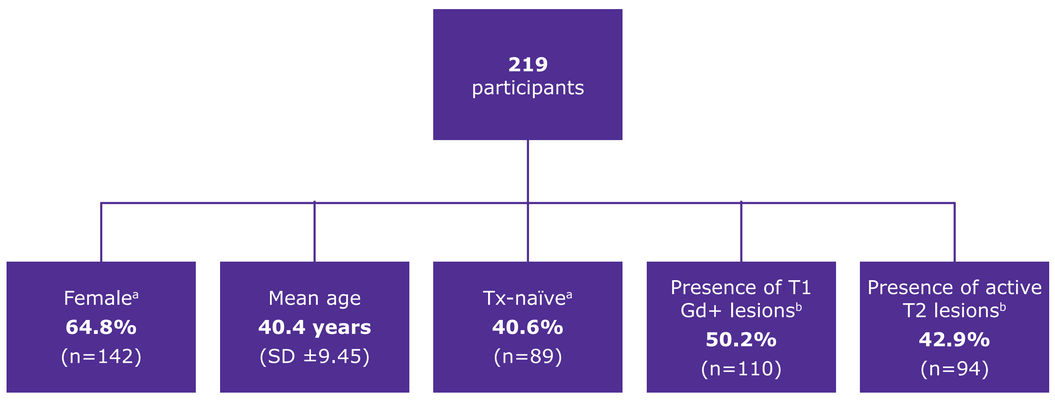
MAGNIFY-MS Extension (NCT04783935) is a 2-year follow-up study that aims to evaluate the long-term effectiveness of short-course cladribine tablets therapy up to 4 years after the initial dose.

METHODS

- Participants were included in MAGNIFY-MS Extension if they received ≥1 dose of cladribine tablets in MAGNIFY-MS (parent study) and had magnetic resonance imaging (MRI) data available from month (M)18 or M24 of the parent study. Expanded Disability Status Scale and relapse data were also required from M24.
- Visits occurred at M36 and M48. Cladribine tablets treatment was not planned in Years 3 or 4.
- Primary endpoint: Proportion of participants with no evidence of disease activity (NEDA-3) in Years 3 and 4 combined (defined as no qualifying relapses, no 6-month confirmed disability progression [6mCDP], and no new T1 gadolinium-enhancing (Gd+) and/or active T2 MRI lesions).
- Data were analysed for all participants combined; subgroups included treatment (Tx)-naive and Tx-experienced participants.

RESULTS

Figure 1. Participant Characteristics at Entry to MAGNIFY-MS Extension



[a]Data recorded at MAGNIFY-MS parent study baseline. [b]Data recorded at MAGNIFY-MS baseline period (the period between the screening and the baseline MRI scan in MAGNIFY-MS study)
Gd+, gadolinium enhancing; MRI, magnetic resonance imaging; SD, standard deviation; Tx, treatment

- A total of 219 participants entered the MAGNIFY-MS extension study at M24 (**Figure 1**). Full participant characteristics are presented in **Supplementary Table 1**.

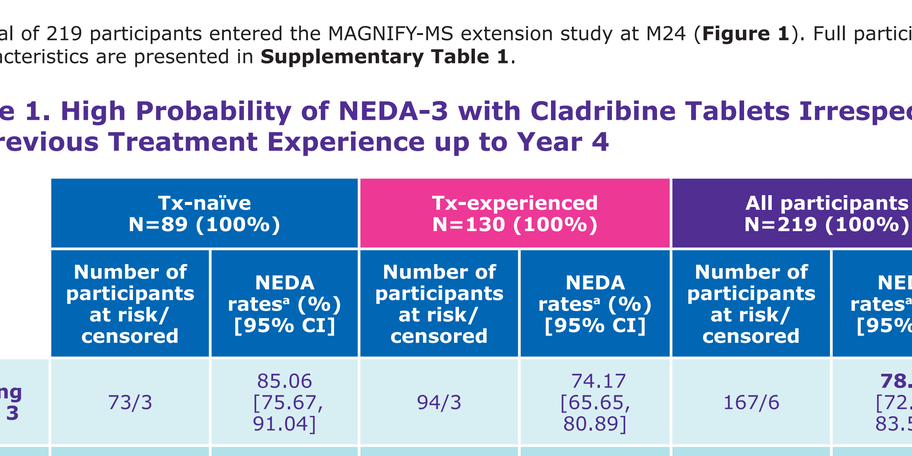
Table 1. High Probability of NEDA-3 with Cladribine Tablets Irrespective of Previous Treatment Experience up to Year 4

	Tx-naïve N=89 (100%)		Tx-experienced N=130 (100%)		All participants N=219 (100%)	
	Number of participants at risk/ censored	NEDA rates[a] (%) [95% CI]	Number of participants at risk/ censored	NEDA rates[a] (%) [95% CI]	Number of participants at risk/ censored	NEDA rates[a] (%) [95% CI]
During Year 3	73/3	85.06 [75.67, 91.04]	94/3	74.17 [65.65, 80.89]	167/6	**78.61** [72.50, 83.52]
During Year 4	41/34	79.79 [67.96, 87.63]	62/45	78.77 [69.60, 85.46]	103/79	**79.20** [72.30, 84.56]

[a]Based on Kaplan–Meier estimates. NEDA rates were estimated from Kaplan–Meier probabilities for absence of all three NEDA-3 components
CI, confidence interval; NEDA, no evidence of disease activity; Tx, treatment

- During the extension period, the Kaplan–Meier-estimated NEDA-3 rate for all participants (95% confidence interval) was 78.6% (72.5, 83.5) in Year 3, 79.2% (72.3, 84.6) in Year 4, and 54.2% (47.3, 60.7) during Years 3 and 4 combined (**Table 1**).
- Crude event proportions for individual NEDA-3 components during Years 3 and 4 are presented in **Supplementary Table 2**.

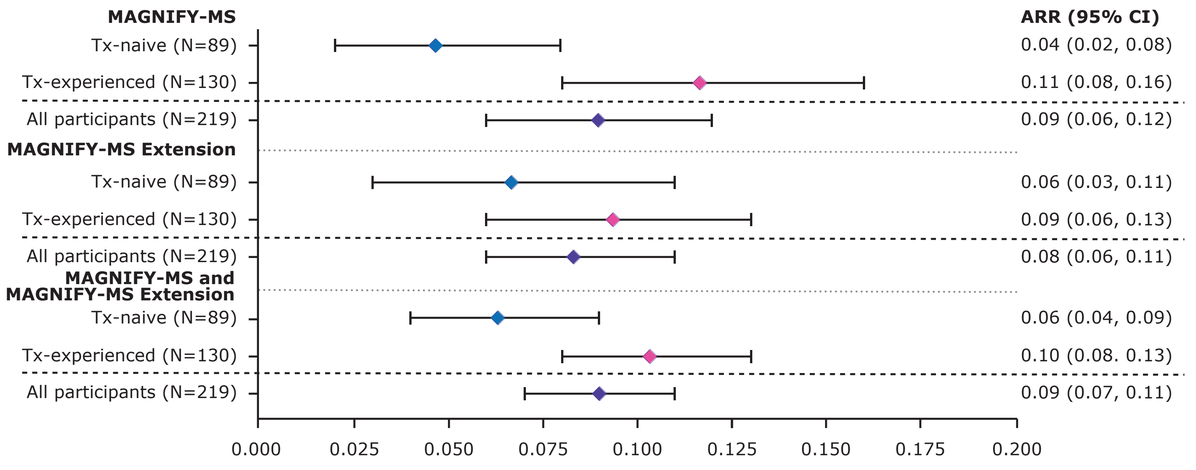
Figure 2. Marked Reductions Versus BL were Observed for T1 Gd+ and Active T2 Lesions Over 4 Years



The baseline period is defined as the period between the screening and BL MRI scan in the MAGNIFY-MS study
BL, baseline; CI, confidence interval; Gd+, gadolinium-enhancing; LS, least square; M, month; MRI, magnetic resonance imaging

- A decrease in T1 Gd+ lesion counts and annualised active T2 lesions was observed at M48 compared to baseline. Overall, 83.1% (n=172) and 67.4% (n=126) had no T1 Gd+ lesions and no active T2 lesions in Year 4, respectively (**Figure 2**).

Figure 3. Low ARRs were Observed Over 4 Years, Especially For Tx-Naive Participants

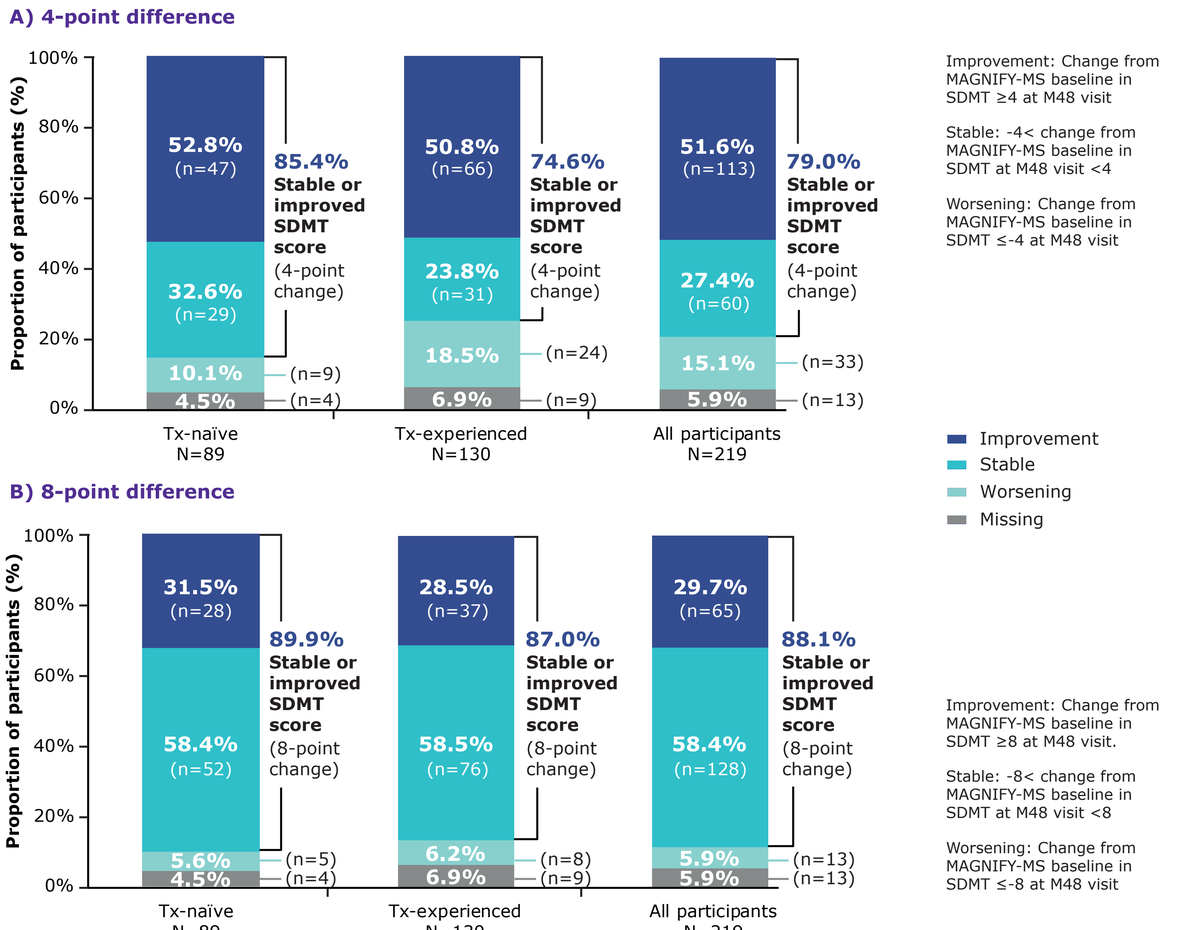


ARR, annualised relapse rate; CI, confidence interval; Tx, treatment

- The low annualised relapse rate (ARR) observed in the parent study (0.09) was maintained in the extension study (0.08) demonstrating the long-term, 4-year high efficacy of cladribine tablets in terms of relapses. The ARR was 0.09 over the 4-year study period (**Figure 3**). Efficacy was consistent between Tx-naïve and Tx-experienced participants.

Figure 4. Cognitive Function was Stable (Or Improved) For Most Participants at Year 4

A) 4-point difference



B) 8-point difference

M, month; SDMT, Symbol Digit Modalities Test; Tx, treatment

- An improvement in Symbol Digit Modalities Test (SDMT) score (4-point difference) was observed in 51.6% of participants overall at M48 after start of cladribine tablets treatment, with 27.4% of participants maintaining a stable SDMT score (**Figure 4A**).
- An improvement in SDMT score (8-point difference) was observed in 29.7% of participants overall at M48 after start of cladribine tablets treatment, with 58.4% of participants maintaining a stable SDMT score (**Figure 4B**).
- There were 142 participants (64.8%) with ≥1 adverse event (AE) during the extension study (94.4% of them were mild to moderate); 13 (5.9%) had ≥1 serious AE, and 3 (1.4%) had ≥1 serious treatment-related AE. No new safety signals were seen (**Supplementary Table 3**).

CONCLUSIONS

- **These results confirm the durable treatment effect of cladribine tablets on standard clinical measures beyond short-term dosing and provide evidence for maintenance of cognitive stability and improvement in the long term up to 4 years.**

SCAN FOR AFFILIATIONS, DISCLOSURES, AND SUPPLEMENTARY MATERIALS

References:
1. Giovannoni G, et al. *Mult Scler.* 2018;24(12):1594–1604
2. Giovannoni G, et al. *Mult Scler.* 2023;29(6):719–730
3. De Stefano N, et al. *Neurol Neuroimmunol Neuroinflamm.* 2022;9(4):e1197

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Supplementary Materials

Supplementary Table 1. Characteristics of MAGNIFY-MS Participants Who Entered MAGNIFY-MS Extension

	Tx-naïve N=89	Tx-experienced N=130	All participants N=219
Female, n (%)[a]	54 (60.7)	88 (67.7)	142 (64.8)
Age at informed consent, mean ± SD (years)[b]	39.3 ± 9.22	41.2 ± 9.57	40.4 ± 9.45
Age ≤40 years at informed consent, n (%)[b]	45 (50.6)	57 (43.8)	102 (46.6)
Time since onset of MS, median (months)	15.84	78.16	53.82
Number of relapses within 12 months prior to baseline, n (%)			
0	0	2 (1.5)	2 (0.9)
1	13 (14.6)	78 (60.0)	91 (41.6)
2	58 (65.2)	45 (34.6)	103 (47.0)
>2	18 (20.2)	5 (3.8)	23 (10.5)
EDSS at baseline, n (%)			
>3	19 (21.3)	32 (24.6)	51 (23.3)
Number of previous DMTs, n (%)[a]			
0	89 (100.0)	0	89 (40.6)
1	0	76 (58.5)	76 (34.7)
2	0	40 (30.8)	40 (18.3)
>2	0	14 (10.8)	14 (6.4)
Presence of any T1 Gd+ lesions, n (%)[c]	44 (49.4)	66 (50.8)	110 (50.2)
Presence of any active T2 lesions, n (%)[c]	34 (38.2)	60 (46.2)	94 (42.9)
Non-evaluable	2 (2.2)	0	2 (0.9)

[a]Data recorded at MAGNIFY-MS parent study baseline. [b]Informed consent for extension study. [c]Data recorded at 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; MS, multiple sclerosis; SD, standard deviation; Tx, treatment

Supplementary Materials

Supplementary Table 2. Freedom From Relapse and 6mCDP were the Most Commonly Met NEDA-3 Components During Years 3 and 4

	Tx-naïve N=89 (100%)	Tx-experienced N=130 (100%)	All participants N=219 (100%)
During Year 3 and 4	**Event proportion, n (%)**		
No relapse	74 (83.1)	103 (79.2)	177 (80.8)
No 6mCDP	78 (87.6)	107 (82.3)	185 (84.5)
No MRI activity	48 (53.9)	68 (52.3)	116 (53.0)

6m-CDP, 6-month confirmed disability progression; MRI, magnetic resonance imaging; NEDA, no evidence of disease activity; SD, standard deviation; Tx, treatment

Supplementary Materials

Supplementary Table 3. Overview of Adverse Events During Extension Study Period

	Tx-naïve N=89	Tx-experienced N=130	All participants N=219
Any AE[a]	59 (66.3)	83 (63.8)	142 (64.8)
Mild	36 (40.4)	51 (39.2)	87 (39.7)
Moderate	19 (21.3)	28 (21.5)	47 (21.5)
Severe	4 (4.5)	4 (3.1)	8 (3.7)
Any study treatment-related AE[a]	11 (12.4)	10 (7.7)	21 (9.6)
Mild	6 (6.7)	5 (3.8)	11 (5.0)
Moderate	4 (4.5)	5 (3.8)	9 (4.1)
Severe	1 (1.1)	0	1 (0.5)
Any serious AE	6 (6.7)	7 (5.4)	13 (5.9)
Any study treatment-related serious AE	2 (2.2)	1 (0.8)	3 (1.4)
Infections (bronchitis)	1 (1.1)	0	1 (0.5)
Infections (peritonsillitis)	0	1 (0.8)	1 (0.5)
Infections (tonsillitis)	0	1 (0.8)	1 (0.5)
Neoplasms (malignant melanoma)	1 (1.1)	0	1 (0.5)
Participants with ≥1 AE[b]			
COVID-19	19 (21.3)	31 (23.8)	50 (22.8)
Headache	8 (9.0)	8 (6.2)	16 (7.3)
Nasopharyngitis	7 (7.9)	8 (6.2)	15 (6.8)
Upper respiratory tract infection	6 (6.7)	6 (4.6)	12 (5.5)
Influenza	6 (6.7)	5 (3.8)	11 (5.0)
Back pain	2 (2.2)	7 (5.4)	9 (4.1)
Pain in extremity	4 (4.5)	4 (3.1)	8 (3.7)
Bronchitis	3 (3.4)	4 (3.1)	7 (3.2)
Nausea	2 (2.2)	4 (3.1)	6 (2.7)
Pregnancy	3 (3.4)	3 (2.3)	6 (2.7)
Lymphopenia	3 (3.4)	2 (1.5)	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; Tx, treatment

Supplementary Materials

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Disclosures

NDS has received honoraria from Biogen, Bristol Myers Squibb, Celgene, Genzyme, Immunic, EMD Serono Research & Development Institute, Inc., Billerica, MA, USA, an affiliate of Merck KGaA, Novartis, Roche and Teva for consulting services, speaking, and travel support. He serves on advisory boards for Merck, Novartis, Biogen, Genzyme, Immunic, and Roche, and has received research grant support from the Italian MS Society.

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HW is member of scientific advisory boards/steering committees for Bayer, Biogen, Merck, Novartis, Roche, Sanofi, and Teva. He received speaker honoraria and travel support from Bayer, Biogen, CSL Behring, EMD Serono Research & Development Institute, Inc., Billerica, MA, USA, an affiliate of Merck KGaA, Fresenius Medical Care, Merck, Omniamed, Novartis, Sanofi, and Teva. He received compensation as a consultant from Biogen, Merck, Novartis, Omniamed, Roche, and Sanofi. He has received research support from Bayer, Biogen, Merck, 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) Münster, and RE Children's Foundation.

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TD serves on scientific advisory boards for Actelion (Janssen/J&J), Bayer, Biogen, Celgene (Bristol Myers Squibb), GeNeuro, MedDay, Merck, Mitsubishi Pharma, Novartis, Roche, and Sanofi; has received funding for travel and/or speaker honoraria from Bayer, Biogen, Merck, Novartis, Roche, and Sanofi; and receives research support from Actelion, the European Union, Novartis, Roche, the Swiss MS Society, and the Swiss National Foundation.

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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 Research & Development Institute, Inc., Billerica, MA, USA, an affiliate of Merck KGaA, Merck, Novartis, Roche, Sanofi, and Teva.

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SH serves on advisory boards for Bayer, Biogen, Merck, Novartis, Roche, and Sanofi. She has received money for travel and speaker honoraria from Bayer, Biogen, Merck, Novartis, Roche, and Sanofi.

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