Durable Effects of Cladribine Tablets on CSF OCB and NfL Over 4 Years in Relapsing Multiple Sclerosis: Results From the MAGNIFY-MS Extension Study

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RESEARCH IN CONTEXT

1. **In this study, participants with disappearance of OCBs had NEDA-3 status and improvements in T25FW. The majority of participants with decrease in OCBs showed improvements in cognition.**
2. **OCBs taken together with clinical parameters and other biomarkers can help with understanding of changes in intrathecal inflammation and disease progression.**

OBJECTIVES

To evaluate the long-term effects of cladribine tablets (CladT) on oligoclonal bands (OCBs) and neurofilament light chain (NfL) levels as markers of inflammation and neuroaxonal damage in the central nervous system (CNS).

INTRODUCTION

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

Findings from the **cerebrospinal fluid (CSF) sub-study of MAGNIFY-MS** (N=28) indicated a beneficial impact of CladT on intrathecal neuroinflammation and neuroaxonal damage.

- In participants with ≥2 OCBs at baseline (BL), **76.5% had reduction or disappearance in OCB counts**.[a1]
- Furthermore, >56% of all participants in the CSF sub-study showed a **reduction in NfL** levels in the CSF at M24.[1]

Here we present OCB and NfL data over the full 4-year treatment period and compare it with clinical outcomes.

[a]At least once post-baseline (at month [M]24).

METHODS

- Participants with highly active relapsing multiple sclerosis who had completed two short-course treatments with CladT in years 1 and 2 of MAGNIFY-MS were eligible to enter this 2-year treatment-free extension study, forming a cumulative observational duration of 4 years.
- NfL levels in serum and CSF are reported as median percentage change from BL at each time point.
- The CSF sub-study reported changes in OCB counts as decreased, increased, no change, or complete disappearance for participants with ≥2 and ≥4 OCBs at BL. Changes in clinical parameters of each participant are considered alongside OCB changes.
- OCB counts and NfL levels were analyzed at BL, M12, M24, M36, and M48 for participants who continued into the Extension study. All statistics are descriptive.

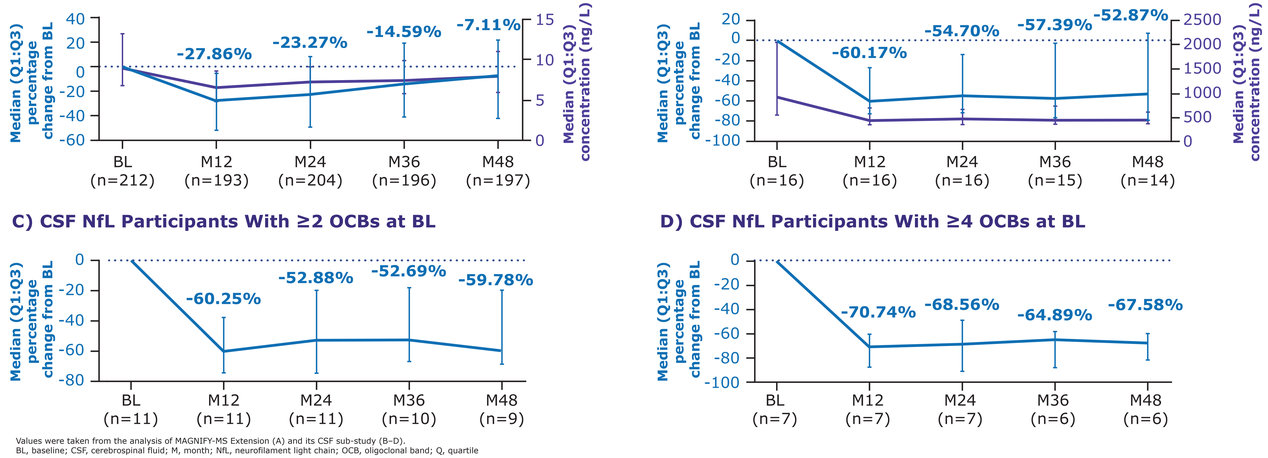
RESULTS

- The MAGNIFY-MS parent study included 270 participants, of which 219 continued into MAGNIFY-MS Extension.
- The MAGNIFY-MS CSF sub-study of the parent study included 28 participants, of which 16 continued into the Extension CSF sub-study (**Supplementary Table 1**).
- Of 16 participants who continued into the MAGNIFY-MS Extension CSF sub-study, 11 had ≥2 OCBs at BL. Among these 11 participants, nine had data for M36 and M48, and seven of these 11 participants had ≥4 OCBs at BL.
  - The majority had decrease or disappearance of OCBs in the study (**Figure 1; Supplementary Figure 1**).

Figure 1. The Majority of Participants[a] With ≥2 OCB at BL (N=11) Had Decrease or Disappearance of OCBs in the Study

Dark purple shows OCB decrease or disappearance; light purple shows stable, increase, or missing data.
[a]Participants who continued into the Extension CSF sub-study.
BL, baseline; M, month; OCB, oligoclonal band

Figure 2. Sustained NfL Reduction in Serum and CSF



Values were taken from the analysis of MAGNIFY-MS Extension (A) and its CSF sub-study (B–D).
BL, baseline; CSF, cerebrospinal fluid; M, month; NfL, neurofilament light chain; OCB, oligoclonal band; Q, quartile

- CSF immunoglobulin (Ig)G and IgM levels were stable for most participants.
- For three participants in the ≥2 OCB group there was no change in OCB counts at M36, and no participants in either group showed increase in OCB counts at M36 or M48 (**Supplementary Figure 1**).
- Two participants had disappearance of OCBs at M48 compared with BL, and both of these achieved no evidence of disease activity (NEDA)-3 (**Supplementary Table 2**).
  - Furthermore, both of these participants showed improvement in the timed 25-foot walk (T25FW; -7.65% and -6.17% change compared with BL).
  - One of these participants showed cognitive improvement, as evaluated by the symbol digit modality test (SDMT; +4), as well as improvement in the 9-hole peg test (9HPT; -10.97% change from BL).
- Four of the six participants with decreased OCBs at M48 had SDMT improvement of ≥4 compared with BL.
  - Two of these six participants achieved NEDA-3 at M48.
- Median NfL levels showed sustained and significant reductions compared with BL in both serum and CSF (**Figure 2**).

The long-term safety profile of CladT was observed to be consistent with earlier safety data, and no new safety signals were observed.

CONCLUSIONS

- **Despite the limitations in sample size, the results suggest that two short courses of CladT provide long-term (persisting into the treatment-free period) reductions in intrathecal neuroinflammation and neuroaxonal damage.**
- **Furthermore, the reduction and disappearance of OCBs was observed in parallel with improvements in clinical parameters: NEDA-3, T25FW, SDMT, and 9HPT, supporting a connection between the reduction in intrathecal inflammation and clinical benefits of CladT.**

SCAN FOR AFFILIATIONS, DISCLOSURES, AND SUPPLEMENTARY MATERIALS

References: 1. De Stefano N, et al. *Int J MS Care*. 2024;26(s1):1.

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Supplementary Materials

Supplementary Table 1. Participant Characteristics

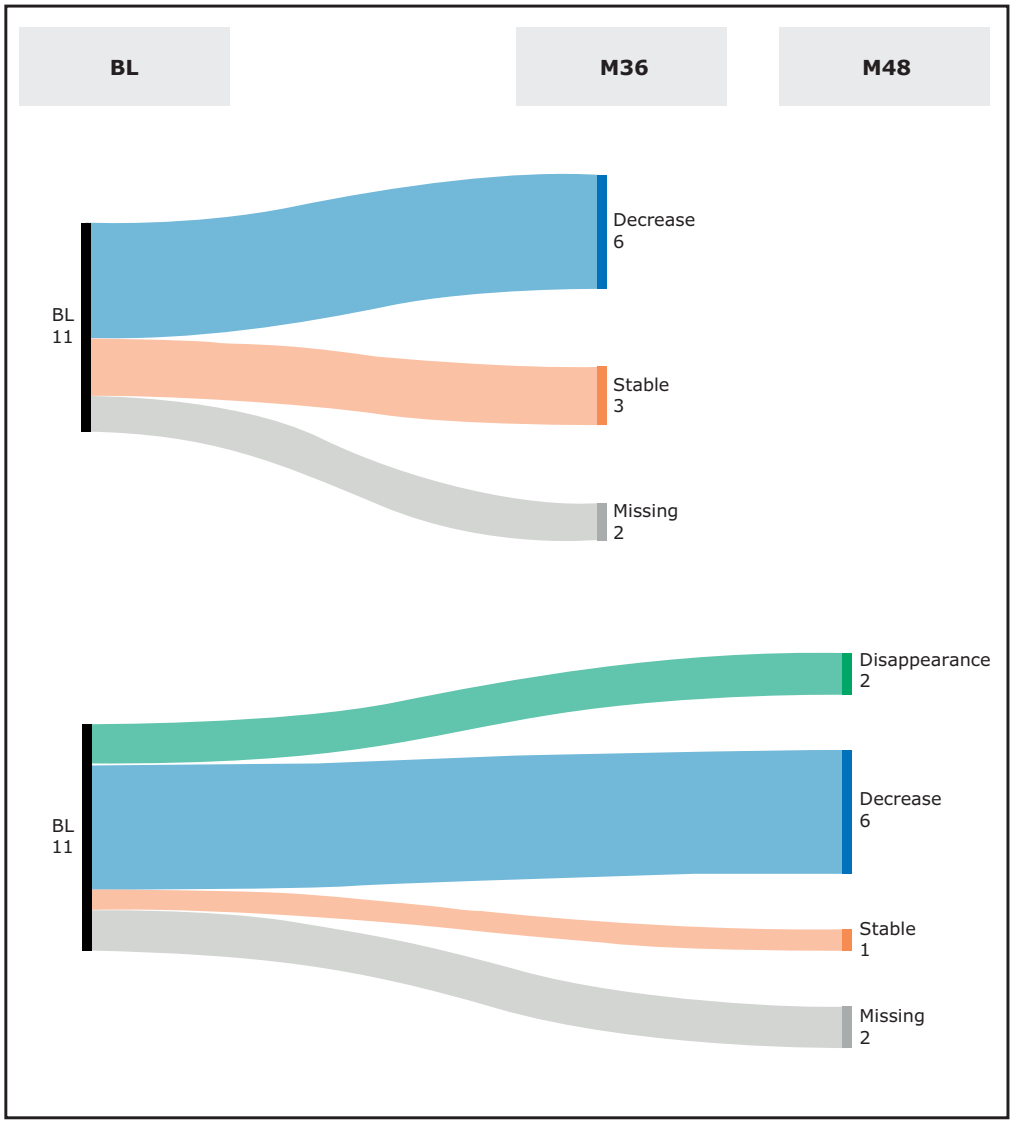
	MAGNIFY-MS		MAGNIFY-MS Extension	
	Parent study (N=270)	CSF sub-study (N=28)	Parent study (N=219)	CSF sub-study (N=16)
Female, n (%)	180 (66.7)	14 (50.0)	142 (64.8)	7 (43.8)
Age, years, mean ± SD	37.7 ± 9.75	36.7 ± 8.26	37.4 ± 9.42	38.1 ± 7.63
Median time since onset of MS, months	55.8	51.5	53.8	11.6
Number of relapses within 12 months prior to MAGNIFY-MS BL, n (%)				
0	3 (1.1)	0 (0.0)	2 (0.9)	0 (0.0)
1	102 (37.8)	8 (28.6)	91 (41.6)	2 (12.5)
2	133 (49.3)	17 (60.7)	103 (47.0)	12 (75.0)
>2	32 (11.9)	3 (10.7)	23 (10.5)	2 (12.5)
EDSS >3 at MAGNIFY-MS BL, n (%)	66 (24.4)	11 (39.3)	51 (23.3)	7 (43.8)
Number of previous DMTs, n (%)[a]				
0	117 (43.3)	14 (50.0)	89 (40.6)	11 (68.8)
1	88 (32.6)	7 (25.0)	76 (34.7)	3 (18.8)
2	50 (18.5)	3 (10.7)	40 (18.3)	1 (6.3)
>2	15 (5.6)	4 (14.3)	14 (6.4)	1 (6.3)
Presence of any T1 Gd+ lesions, n (%)[b]	136 (50.4)	13 (46.4)	110 (50.2)	9 (56.3)
Presence of any active T2 lesions, n (%)[b]	113 (41.9)	11 (39.3)	94 (42.9)	8 (50.0)
Non-evaluable	2 (0.7)	0 (0.0)	2 (0.9)	0 (0.0)
Missing	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)

[a]DMTs (retrieved from parent study) are counted by participant. [b]During the MAGNIFY-MS BL period (median BL period [screening – BL] had a duration of 35.0 days [range 16–92]).
BL, baseline; CSF, cerebrospinal fluid; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; MS, multiple sclerosis; SD, standard deviation

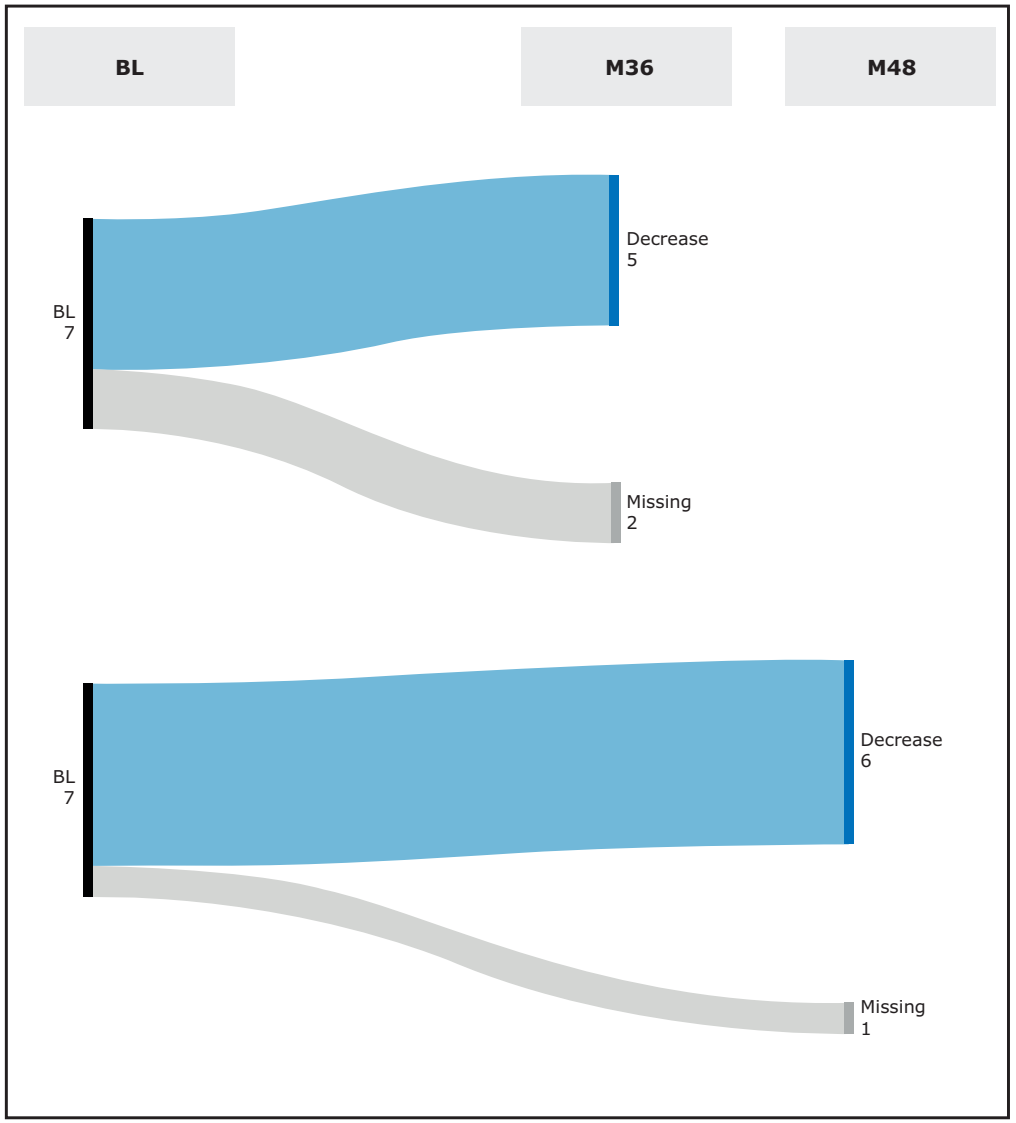
Supplementary Materials

Supplementary Figure 1. No Participants Had Increased OCB Counts at M36 or M48 Compared With BL

A) Number of Participants With ≥2 OCBs at BL



B) Number of Participants With ≥4 OCBs at BL



BL, baseline; M, month; OCB, oligoclonal band

Supplementary Materials

Supplementary Table 2. Clinical Outcomes in Participants With ≥2 OCBs at BL, by OCB Change From BL to M48 (N=11)

Participant number	T1 Gd+ lesion count[a]	Active T2 lesion count[a]	9HPT		T25FW		SDMT		NEDA-3 achieved
			Mean time (seconds)	% change from BL	Mean time (seconds)	% change from BL	Score	Score change from BL[b]	
Disappearance (n=2)									
1	0	0	30.1	3.79	7.9	-7.65	50	0	YES
2	0	0	19.7	-10.97	3.8	-6.17	59	4	YES
Decrease (n=6)									
3	2	2	25.6	13.64	6.1	19.61	61	8	NO
4	0	1	23.2	8.94	5.7	10.78	65	10	NO
5	0	0	23.7	0.11	5.5	8.91	55	4	YES
6	0	2	20.9	-5.42	3.7	17.46	57	0	NO
7	0	1	31.5	19.90	6.1	0.00	42	5	NO
8	0	0	25.6	16.12	6.7	31.37	54	2	YES
Stable (n=1)									
9	3	6	24.9	-10.28	6.1	3.42	53	12	NO
Missing (n=2)									
10	0	0	25.7	5.77	5.7	22.58	55	13	YES
11	0	7	27.7	10.82	6.3	10.62	51	6	NO

[a]Count at M48 (independent from BL). [b]SDMT score change of ≥4 reflects notable improvement.
9HPT, 9-hole peg test; BL, baseline; Gd+, gadolinium-enhancing; M, month; NEDA, no evidence of disease activity; OCB, oligoclonal band; SDMT, symbol digit modality test; T25FW, timed 25-foot walk

Supplementary Materials

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