Effect of Cladribine Tablets on Markers of Disease Progression, Axonal Loss and Oligoclonal Bands in Patients With Relapsing Multiple Sclerosis: Results from MAGNIFY-MS

N. De Stefano[1], A. Achiron[2,3], F. Barkhof[4,5], A. Chan[6], T. Derfuss[7], S. Hodgkinson[8], L. Leocani[9–11], X. Montalban[12,13], A. Prat[14], K. Schmierer[15,16], F. Sellebjerg[17,18], P. Vermersch[19], H. Wiendl[20], A. Chudecka[21], L. Gardner[22]

[1]Department of Medicine, Surgery and Neuroscience, University of Siena, Siena, Italy; [2]Multiple Sclerosis Center, Sheba Academic Medical Center, Ramat Gan, Israel; [3]Sackler School of Medicine, Tel-Aviv University, Israel; [4]Department of Radiology and Nuclear Medicine, Amsterdam UMC, Vrije Universiteit, Amsterdam, The Netherlands; [5]Queen Square Institute of Neurology and Centre for Medical Image Computing, University College London, London, UK; [6]Department of Neurology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland; [7]Department of Neurology, University Hospital Basel, Basel, Switzerland; [8]Ingham Institute for Applied Medical Research, University of New South Wales Medicine and Liverpool Hospital, Sydney, NSW, Australia; [9]University Vita-Salute San Raffaele, Milan, Italy; [10]Scientific Institute IRCCS San Raffaele, Milan, Italy; [11]Department of Neurorehabilitation Science, Casa di Cura Igea, Milan, Italy; [12]Division of Neurology, St Michael's Hospital, University of Toronto, Toronto, ON, Canada; [13]Department of Neurology, Centre d'Esclerosi Múltiple de Catalunya (Cemcat), Hospital Universitario Vall d'Hebron, Universitat Autonoma de Barcelona, Barcelona, Spain; [14]Department of Neurosciences, Université de Montréal, Montréal, QC, Canada; [15]The Blizard Institute, Centre for Neuroscience, Surgery and Trauma, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK; [16]Clinical Board Medicine (Neuroscience), The Royal London Hospital, Barts Health NHS Trust, London, UK; [17]Danish MS Center, Department of Neurology, Copenhagen University Hospital - Rigshospitalet, Glostrup, Denmark; [18]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark; [19]Univ. Lille, Inserm U1172 LilNCog, CHU Lille, FHU Precise, Lille, France; [20]Department of Neurology with Institute of Translational Neurology, University of Münster, Münster, Germany; [21]Cytel Inc., Geneva, Switzerland; [22]EMD Serono, Billerica, MA, USA

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He serves as associate editor of the European Journal of Neurology, on the editorial board for Clinical and Translational Neuroscience and as topic editor for the Journal of International Medical Research. **T. Derfuss** serves on scientific advisory boards for Actelion (Janssen/J&J), Bayer, Biogen, Celgene (Bristol Myers Squibb), GeNeuro, MedDay, the healthcare business of Merck KGaA, Darmstadt, Germany, Mitsubishi Pharma, Novartis, Roche, and Sanofi; has received funding for travel and/or speaker honoraria from Biogen, the healthcare business of Merck KGaA, Darmstadt, Germany, Novartis, Roche, and Sanofi; and receives research support from Actelion, the European Union, Novartis, Roche, the Swiss MS Society, and the Swiss National Foundation. **S. Hodgkinson** serves on advisory boards for Bayer, Biogen, the healthcare business of Merck KGaA, Darmstadt, Germany, Novartis, Roche, and Sanofi. 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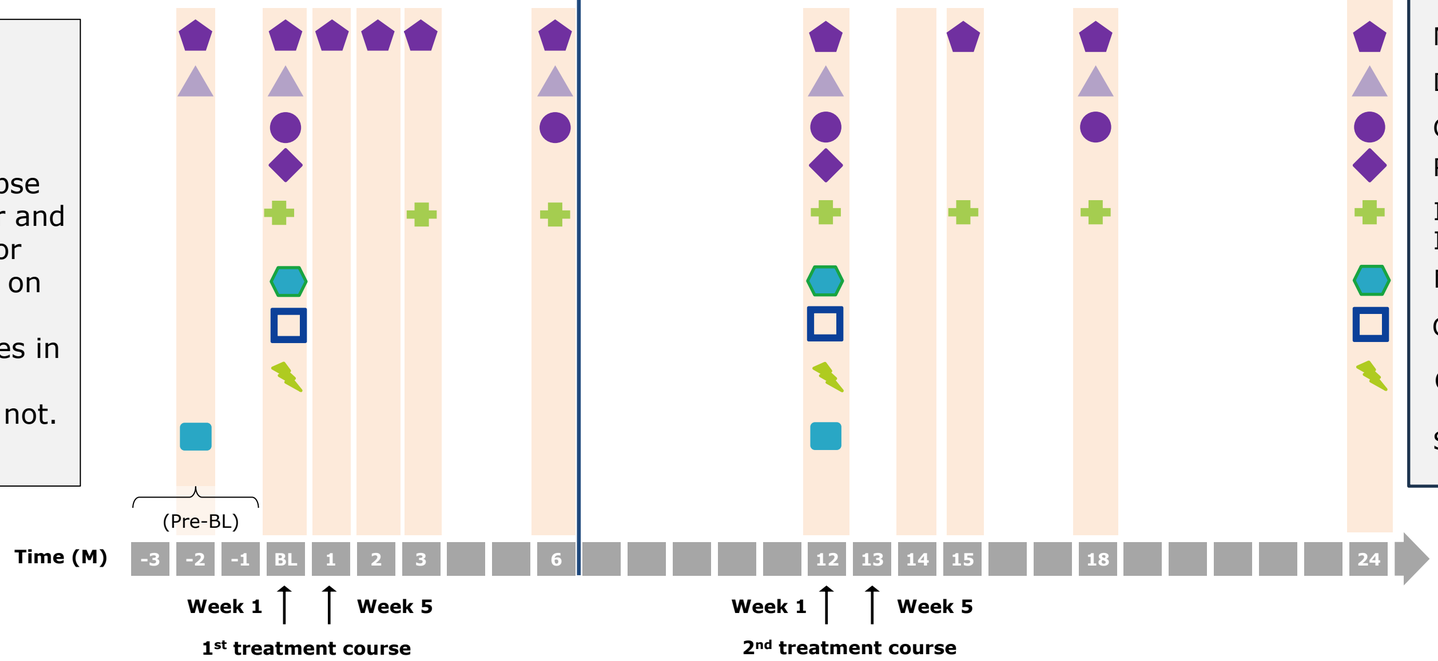
INTRODUCTION AND STUDY DESIGN

The phase IV MAGNIFY-MS (NCT03364036) study investigated onset of action and sustained efficacy of cladribine tablets (3.5 mg/kg cumulative dose over 2 years) in highly active RMS.[1-3] Exploratory sub-studies assessed disease activity by OCT, and biomarkers in CSF and blood.

Primary endpoint
Difference in the counts of CUA MRI lesions at the end of 6 months compared to BL Period

Key Inclusion Criteria:

Population:
Highly active RMS, defined as one relapse in the previous year and ≥1 T1 Gd+ lesion, or ≥9 T2 lesions while on therapy with other DMTs; or ≥2 relapses in the previous year whether on DMT or not.



- MRI
- Disability (EDSS/KFS, 9HPT, T25FW)
- Cognition (SDMT)
- Relapse count
- Immune cell subtypes and Immunoglobulins
- NfL
- CSF Sub-study
- OCT Sub-study
- Safety*

*Safety includes TB – active & latent; Hepatitis B & C; HIV; Pregnancy.

1. De Stefano N, et al. *Neurol Neuroimmunol Neuroinflamm*. 2022;9(4):e1187. 2. Wiendl H, et al. *Neurol Neuroimmunol Neuroinflamm*. 2022;10(1):e200048. 3. Wiendl H, et al. *Neurology*. 2023;100(17_Supplement_2):3016.

9HPT, 9-hole peg test; **BL**, baseline; **CFS**, cerebrospinal fluid; **CUA**, combined unique active; **DMT**, disease-modifying therapy; **EDSS**, Expanded Disability Status Scale; **Gd+**, gadolinium-enhancing; **HIV**, human immunodeficiency virus; **KFS**, Kurtzke Functional System; **M**, month; **MRI**, magnetic resonance imaging; **NfL**, neurofilament light chain; **OCT**, optical coherence tomography; **RMS**, relapsing multiple sclerosis; **SDMT**, Symbol Digit Modalities Test; **T25FW**, timed 25-foot walk; **TB**, tuberculosis

Cladribine tablets 10 mg (3.5 mg/kg cumulative dose over 2 years) are indicated for the treatment of people with MS in the United States (relapsing forms of MS, including relapsing-remitting disease and active secondary progressive disease, in adults).

Data collection and analysis was sponsored by the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945)

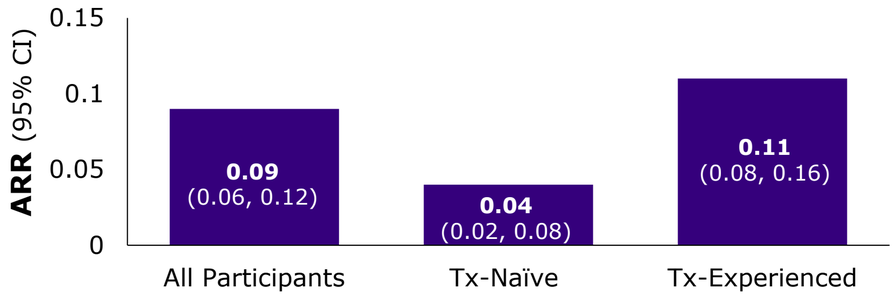
RESULTS of the MAIN STUDY [1]

For the main study, during the 2-year treatment period:

RELAPSES

83% (224/270) of participants did not have a qualifying relapse. Of those with at least one qualifying relapse, most participants (37/46) had a single relapse.

ARR during the 2-year study period*



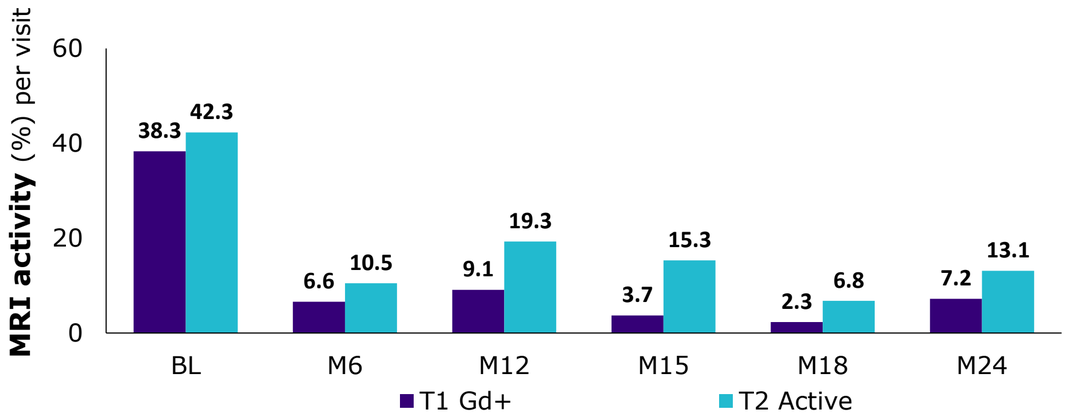
DISABILITY MEASURES

Most participants showed no relevant progression in T25FW or 9HTP.

Measures of disease progression	Total N=270 (%)
No T25FW progression	**234 (86.7)**
No 9HPT progression	**247 (91.5)**
No 6mCDP	**236 (87.4)**
Unknown status	**13 (4.8)**

MRI

Percentage of participants with 6-monthly MRI readouts



Mean T1 Gd+ and annualized active T2 lesion counts were markedly reduced and sustained through to M24.

SAFETY

No new safety signals were observed.

The most common TEAEs were headache (32.2%), nasopharyngitis (21.1%), urinary tract infection (11.9%), fatigue (11.5%), and nausea (11.5%).

1. De Stefano, N, et al. *Int J MS Care*. 2023;25(1):38–39 (poster DMT44). *ARR data have not been presented previously, and are calculated for N=219 participants who entered the extension study.
6mCDP, 6-month confirmed disability progression; **9HPT**, 9-hole peg test; **ARR**, annualized relapse rate; **BL**, baseline; **CI**, confidence interval; **Gd+**, gadolinium-enhancing; **M**, month; **MRI**, magnetic resonance imaging; **T25FW**, timed 25-foot walk; **TEAE**, treatment-emergent adverse event; **Tx**, treatment

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OBJECTIVE AND METHODS

Objective: Evaluate the effect of cladribine tablets on disease activity in the periphery and biomarkers in the CNS

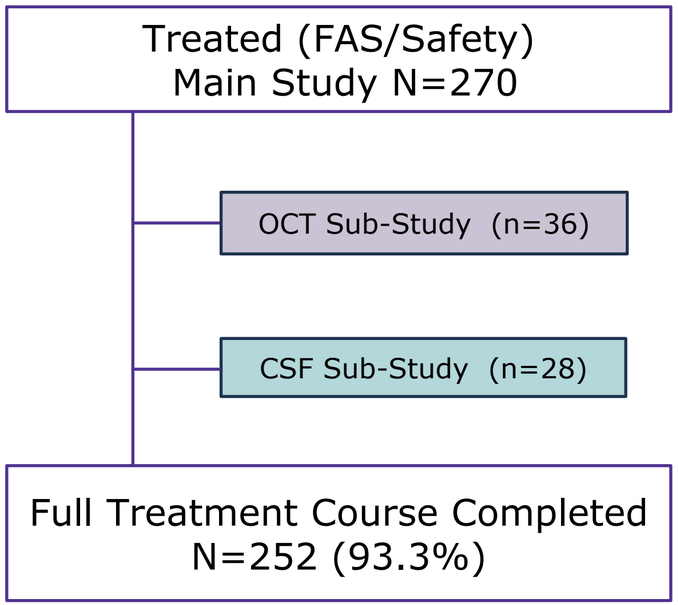
METHODS (all analyses were exploratory)

Main study:

- NEDA-3 and NEPAD were calculated for 270 participants with available data in two treatment periods: **Year 1) post-BL to M12**, and **Year 2) post-M12 to M24** using logistic regression adjusting for age and EDSS score at BL (>3, ≤3).

Sub studies:

- For **OCT** (N=36) and **CSF** (N=28) sub-studies participants gave additional informed consent.
- **OCT** was performed on both eyes using thickness measurements of RNFL, GCL/IPL, macular and its sectors (on Zeiss or Heidelberg Spectralis machines).
- Change in low contrast letter acuity scores and contrast sensitivity visual acuity scores were assessed.
- Changes in **OCBs** were described as either **decrease or complete disappearance** for participants with ≥2 OCB at BL; and percentage change from BL for CSF NfL and CSF Igs.
- Assessments for both sub-studies were performed at BL, M12, and M24.



BL, baseline; **CSF**, cerebrospinal fluid; **CNS**, central nervous system; **EDSS**, Expanded Disability Status Scale; **FAS**, full analysis set; **GCL/IPL**, ganglion cell layer/inner plexiform layer; **Ig**, immunoglobulin; **M**, month; **NEDA**, No Evidence of Disease Activity; **NEPAD**, No Evidence of Progression or Active Disease; **NfL**, neurofilament light chain; **OCB**, oligoclonal band; **OCT**, optical coherence tomography; **RNFL**, retinal nerve fiber layer

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Presented at CMSC 2024 | May 29–June 1 | Nashville, TN, USA

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MAGNIFY MS

RESULTS

Baseline Demographics and Characteristics

	Main study population (N=270)	CSF sub-study population (n=28)	OCT sub-study population (n=36)
Female, n (%)	180 (66.7)	14 (50.0)	25 (69.4)
Aged ≤40 years, n (%)	152 (56.3)	17 (60.7)	15 (41.7)
Time since MS diagnosis in M, mean ± SD	**60.87** ± 74.489	**38.41** ± 61.042	**105.70** ± 91.380
Number of relapses within 12M prior to BL, n (%)			
0	3 (1.1)	0 (0)	1 (2.8)
1	102 (37.8)	8 (28.6)	17 (47.2)
2	133 (49.3)	17 (60.7)	14 (38.9)
>2	32 (11.9)	3 (10.7)	4 (11.1)
EDSS score >3 at BL, n (%)	66 (**24.4**)	11 (**39.3**)	10 (**27.8**)
≥2 previous DMTs, n (%)	65 (24.1)	7 (25.0)	11 (30.6)
Tx-Naïve (%)	117 (43.3)	14 (50.0)	5 (13.9)
Mean T1 Gd+ lesion count for the BL period, ≥1 (%)	136 (**50.4**)	13 (**46.4**)	17 (**47.2**)
Active T2 lesion count (without T1 Gd+) for the BL period, ≥1 (%)	68 (**25.2**)	9 (**32.1**)	5 (**13.9**)

- Participants were enrolled between May 28, 2018 and April 23, 2019, with database lock on December 20, 2021.
- In total, 270 participants were included in the **main MAGNIFY-MS study**: 67% female, 56% aged ≤40 years, and 43% Tx-Naïve.

BL, baseline; **CSF**, cerebrospinal fluid; **DMT**, disease-modifying therapy; **EDSS**, Expanded Disability Status Scale; **Gd+**, gadolinium-enhancing; **M**, month; **MS**, multiple sclerosis; **OCT**, optical coherence tomography; **SD**, standard deviation; **Tx**, treatment

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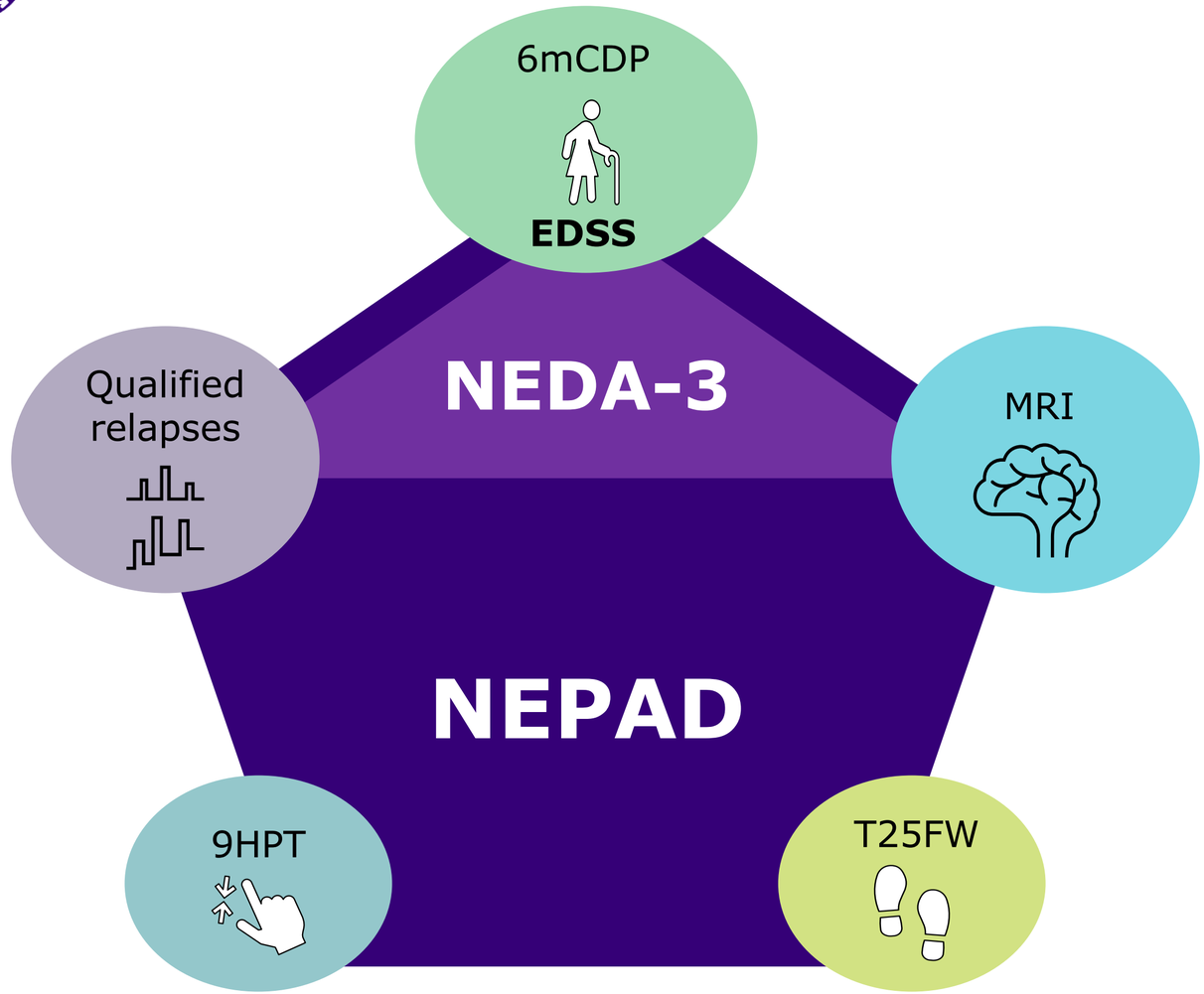
MAIN STUDY: NEDA-3 and NEPAD



NEDA-3: No **E**vidence of **D**isease **A**ctivity, was defined as an absence of; 1) qualified relapses, 2) 6mCDP, and 3) MRI activity (T1 Gd^+ or active T2 lesions)

NEPAD: No **E**vidence of **P**rogression or **A**ctive **D**isease, was defined as NEDA-3 with the addition of absence of 20% progression on both the T25FW and 9HPT

6mCDP, 6-month confirmed disability progression; **9HPT**, 9-hole peg test; **BL**, baseline; **EDSS**, Expanded Disability Statius Scale; **Gd+**, gadolinium-enhancing; **M**, month; **MRI**, magnetic resonance imaging; **NEDA**, No Evidence of Disease Activity; **T25FW**, timed 25-foot walk; **Tx**, treatment

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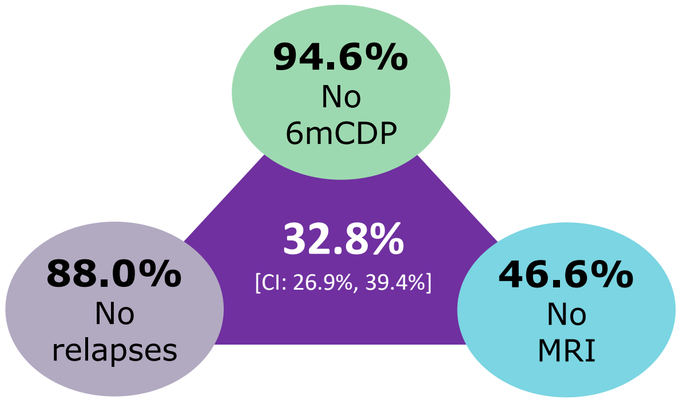
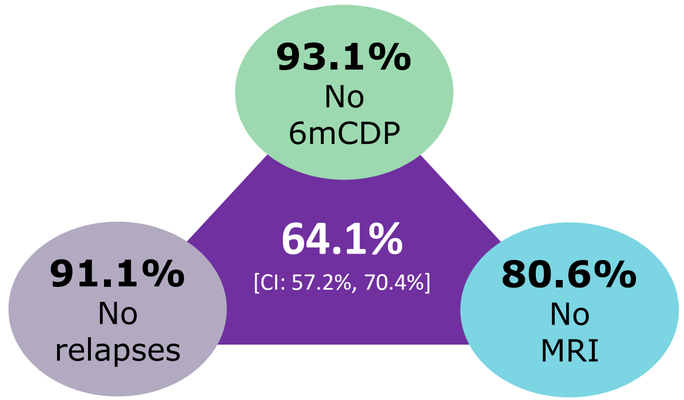
MAIN STUDY: NEDA-3

NEDA-3 was calculated using logistic regression with adjustment for age and EDSS score at BL (>3, ≤3) for all study participants and per group: Tx-Naïve, Tx-Experienced by yearly periods

	Year 1	Year 2
All Participants		
Tx-Naïve	**43.0%** (89.2% no relapses, NE% no 6mCDP, 51.7% no MRI)	**69.1%** (96.9% no relapses, 95.4% no 6mCDP, 78.4% no MRI)
Tx-Experienced	**24.9%** (87.3% no relapses, 92.2% no 6mCDP, 42.7% no MRI)	**60.2%** (88.4% no relapses, 91.9% no 6mCDP, 82.7% no MRI)

The effect of the **full 2-year cladribine tablets dose** was pronounced by a substantial NEDA-3 rate increase during Y2 in each of the groups: NEDA-3 rates were **64.1% overall** and higher for **Tx-Naïve (69.1%)** compared with **Tx-Experienced (60.2%)** participants.

6mCDP, 6-month confirmed disability progression; **BL**, baseline; **CI**, confidence interval; **EDSS**, Expanded Disability Status Scale; **MRI**, magnetic resonance imaging; **NE**, not estimable; **NEDA**, No Evidence of Disease Activity; **Tx**, treatment; **Y**, year

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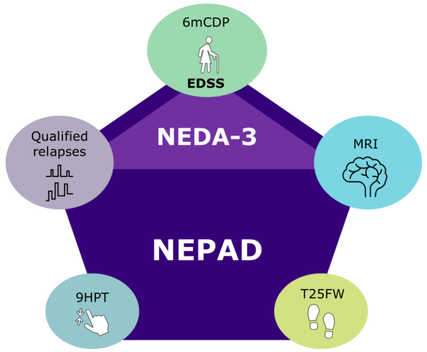
MAIN STUDY: NEPAD



	Year 1	Year 2
All Participants	94.6% No 6mCDP; 88.0% No relapses; 46.6% No MRI; 32.1%; 100% No 9HPT; 97.3% No T25FW	93.1% No 6mCDP; 91.1% No relapses; 80.6% No MRI; 60.2%; 99.0% No 9HPT; 95.4% No T25FW
Tx-Naïve	**43.0%** (89.2% no relapses, NE% no 6mCDP, 51.7% no MRI, 100% no 9HPT, NE% no T25FW)	**67.8%** (96.9% no relapses, 95.4% no 6CDP, 78.4% no MRI, NE% no 9HPT, 97.3% no T25FW)
Tx-Experienced	**23.9%** (87.3% no relapses, 92.2% no 6CDP, 42.7% no MRI, NE% no 9HPT, 95.5% no T25FW)	**54.4%** (88.4% no relapses, 91.9% no 6mCDP, 82.7% no MRI, 98.6% no 9HPT, 95.6% no T25FW)

The effect of the **full 2-year cladribine tablets dose** was pronounced by a substantial NEPAD rate increase during Y2 in each of the groups: NEPAD rates were **60.2% overall** and higher for **Tx-Naïve (67.8%)** compared with **Tx-Experienced (54.4%)** participants.

6mCDP, 6-month confirmed disability progression; **9HPT**, 9-hole peg test; **CI**, confidence interval; **MRI**, magnetic resonance imaging; **NE**, not estimable; **NEDA**, No Evidence of Disease Activity; **NEPAD**, No Evidence of Progression or Active Disease; **T25FW**, timed 25-foot walk; **Tx**, treatment; **Y**, year

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MAGNIFY MS

RESULTS: OCT sub-study

Absolute OCT Measurements and Changes From BL, N=36

Mean ± SD	BL	M12		M24	
	Absolute n=32 (88.9%)	Absolute n=35* (97.2%)	Change from BL n=31* (86.1%)	Absolute n=23 (67.6%)	Change from BL n=21 (61.8%)
RNFL, µm	87.3 ± 13.7	86.7 ± 13.5	-1.4 ± 1.9	86.9 ± 15.8	-3.0 ± 2.4
GCL/IPL thickness, µm:					
Inferior	71.7 ± 9.8	70.8 ± 10.4	-0.2 ± 1.2	71.9 ± 10.3	-0.3 ± 1.4
Inferonasal	73.8 ± 11.0	73.3 ± 11.8	0.6 ± 3.5	74.7 ± 11.6	0.6 ± 4.2
Inferotemporal	73.3 ± 10.1	72.5 ± 10.9	0.1 ± 1.3	73.5 ± 11.6	-0.1 ± 1.9
Superior	73.7 ± 10.0	73.1 ± 10.6	0.4 ± 3.7	74.5 ± 10.5	0.9 ± 4.3
Supranasal	74.4 ± 11.3	73.8 ± 11.9	0.6 ± 3.6	75.2 ± 11.4	0.3 ± 4.3
Supratemporal	72.8 ± 10.0	72.2 ± 10.7	0.2 ± 1.3	73.1 ± 11.6	0.1 ± 1.6

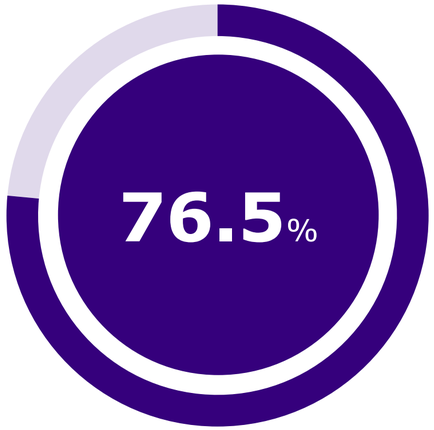
- No changes were observed in measured OCT parameters from BL to M24, suggesting the absence of RNFL thinning over 2 years.
- Improvement in low contrast letter acuity score was observed at M24 (6.3 at 1.25% contrast; 3.8 at 2.5% contrast; *detailed data not shown*).

*For RNFL: n=34 (94.4%) at M12 and n=30 (83.3%) for Change from BL to M12. A limitation of the analyses in the OCT sub-study was the small sample size, so these results should be interpreted with caution.
BL, baseline; **GCL/IPL**, ganglion cell layer/inner plexiform layer; **M**, month; **OCT**, optical coherence tomography; **RNFL**, retinal nerve fiber layer; **SD**, standard deviation

Data collection and analysis was sponsored by the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945)

RESULTS: CSF sub-study

Disappearance/Changes in OCB Counts of Participants Positive For ≥2 OCBs at BL, n=17



OCBs were reduced or eliminated at least once at post-BL visits (M12, M24) in 13 of 17 (76.5%) participants

- **Complete OCBs disappearance** was seen in **11.8%** (2/17) from BL to M12 and was maintained for one participant (5.9%) to M24.
- **Partial OCB disappearanc**es were observed in **64.7%** (11/17) participants at any of the post-Baseline visits: M12 or M24.
- Extension study data will be upcoming in the future

A limitation of the analyses in the CSF sub-study was the small sample size, so these results should be interpreted with caution.
BL, baseline; **CI**, confidence interval; **M**, month; **OCB**, oligoclonal band

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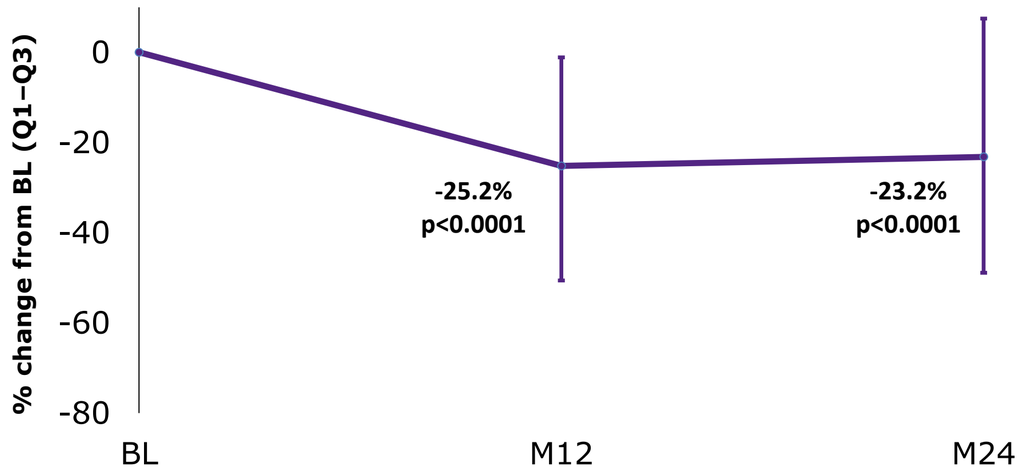
Data collection and analysis was sponsored by the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945)

RESULTS: NfL

Serum NfL change from BL (N=270)



Median (Q1; Q3)	BL	M12	M24
Absolute value, ng/L	**8.89** (6.61; 13.01)	**6.60** (5.05; 8.64)	**7.02** (5.44; 8.86)

CSF NfL change from BL (n=28)

Median (Q1; Q3)	BL	M12	M24
Absolute value, ng/L	**757.15** (410.75; 2012.95)	**385.60** (259.80; 541.10)	**459.40** (336.30; 505.60)

Substantial and sustained reduction in NfL was observed in serum (>20%) and CSF (>55%).

BL, baseline; **CSF**, cerebrospinal fluid; **M**, month; **NfL**, neurofilament light chain; **Q**, quartile

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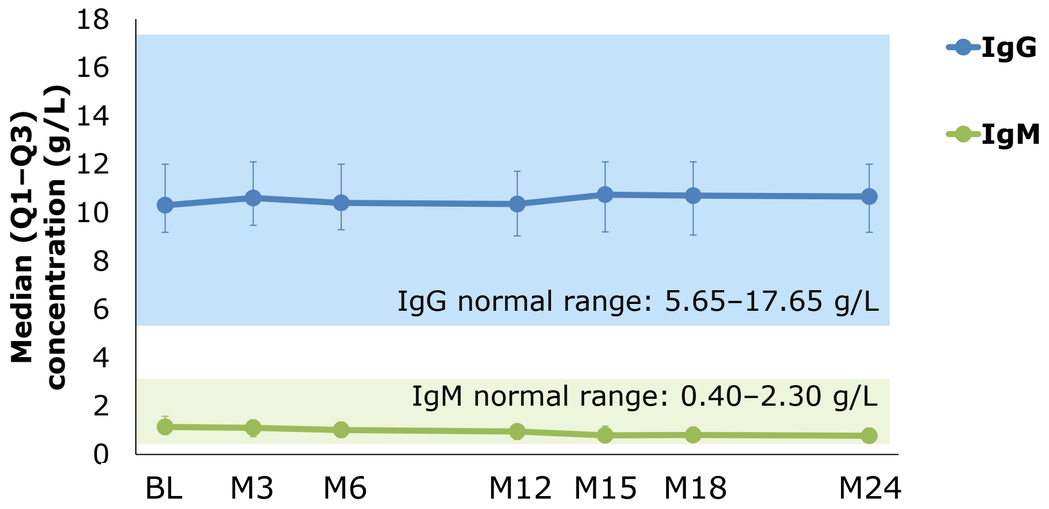
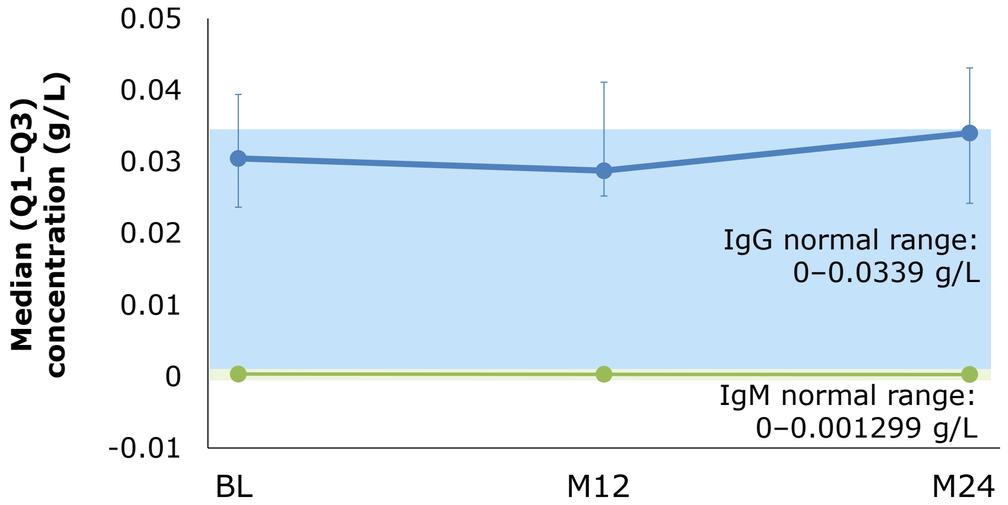
RESULTS: Immunoglobulins

Serum IgG and IgM concentration (N=270)



CSF IgG and IgM concentration (n=28)



Both serum and CSF median IgG and IgM remained within normal range.

BL, baseline; **CSF**, cerebrospinal fluid; **Ig**, immunoglobulin; **LLN**, lower limit of normal; **M**, month; **Q**, quartile

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RESULTS: Safety

Overview of Treatment-Emergent Adverse Events – Safety Analysis Set

Number of Participants with:	Total N=270 (%)
Any TEAE*	227 (84.1)
Mild	114 (42.2)
Moderate	103 (38.1)
Severe	10 (3.7)
Any study treatment-related TEAE*	122 (45.2)
Mild	71 (26.3)
Moderate	47 (17.4)
Severe	4 (1.5)
Any serious TEAE	14 (5.2)
Any study treatment-related serious TEAE	0 (0.0)
Any TEAE leading to **temporary** discontinuation of study treatment	**4 (1.5)**
Any TEAE leading to **permanent** discontinuation of study treatment	1 (0.4)

Participants with ≥1 TEAE	Total N=270 (%)
Headache	87 (32.2)
Nasopharyngitis	57 (21.1)
Urinary tract infection	32 (11.9)
Fatigue	31 (11.5)
Nausea	31 (11.5)
Back pain	30 (11.1)
Lymphopenia	28 (10.4)
Upper respiratory tract infection	27 (10.0)
Diarrhea	26 (9.6)
Pain in extremity	22 (8.1)
Alopecia	21 (7.8)
Dizziness	20 (7.4)

No new safety signals were observed in the study.

*Worst severity per participant is reported.
TEAE, treatment-emergent adverse event

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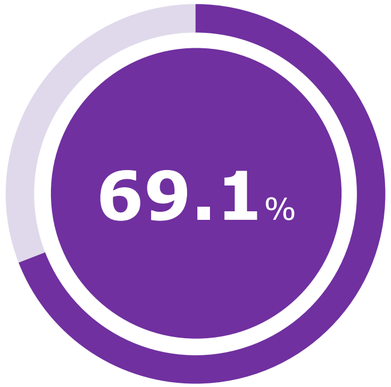
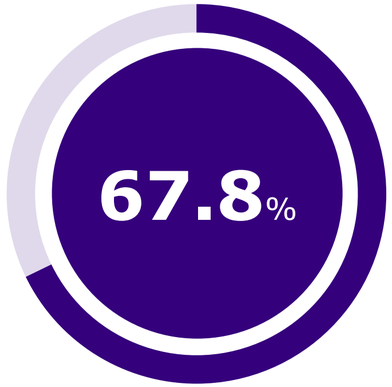
CONCLUSIONS

- NEDA-3 and NEPAD data provide evidence **for a substantial impact of cladribine tablets on disease activity and progression.**
  - **Tx-Naïve participants** had the highest rates of **NEDA-3** and **NEPAD** at the end of Year 2.



NEDA-3



NEPAD

NEDA, No Evidence of Disease Activity; **NEPAD**, No Evidence of Progression or Active Disease; **Tx**, treatment

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CONCLUSIONS

- **Cladribine tablets may have a positive effect on neuroaxonal damage in the periphery and in the CNS** as indicated by significant and sustained **reduction in NfL levels in both serum and CSF** as well as **absence of RNFL thinning.**
- **Reduction or complete disappearance** of oligoclonal bands seen in **76.5% of participants in CSF sub-study** suggest a direct effect of cladribine tablets within the CNS.
- **IgG and IgM levels in both serum and CSF remained within normal ranges** indicating preserved ability to mount an immune response.
- The safety profile of cladribine tablets was consistent with previous reports and no new safety signals were observed.

CNS, central nervous system; **CSF**, cerebrospinal fluid; **Ig**, immunoglobulin; **NfL**, neurofilament light chain; **RNFL**, retinal nerve fiber layer

Cladribine tablets 10 mg (3.5 mg/kg cumulative dose over 2 years) are indicated for the treatment of people with MS in the United States (relapsing forms of MS, including relapsing-remitting disease and active secondary progressive disease, in adults).

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CONCLUSIONS

Overall, the results from MAGNIFY-MS support the early use of cladribine tablets for maximum benefit.

Results from MAGNIFY-MS extension study will be presented in the future.

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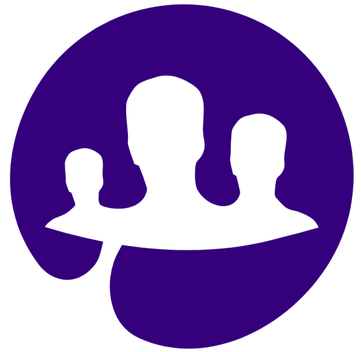
THANK YOU

The study team and members of the steering committee would like to thank all the study participants, family members, caregivers, and staff at all study sites.

THANK YOU!



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