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Two-Year Findings on the Safety and Efficacy of Cladribine Tablets after Treatment with Natalizumab (CLADRINA Trial)

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This work was sponsored by EMD Serono (CrossRef Funder ID: 10.13039/100004755).

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RESEARCH IN CONTEXT

The 2-year CLADRINA study demonstrates that patients with relapsing multiple sclerosis (MS) who quickly transition from natalizumab (NTZ) to cladribine tablets (CladT) maintain disease stability. The study also confirms that CladT is an effective and safe treatment option, with no cases of progressive multifocal leukoencephalopathy (PML) or disease rebound observed.

OBJECTIVES

The CLADRINA study reports data on effectiveness, safety (including lymphocyte dynamics), and MS Disease Activity (MSDA) score over 24 months after switching to cladribine tablets (CladT) from natalizumab (NTZ) within 1 month of their last infusion.

INTRODUCTION

NTZ, a highly effective (HE) therapy approved for relapsing multiple sclerosis (RMS), is associated with an increased risk of developing progressive multifocal leukoencephalopathy (PML) and disease reactivation upon cessation[1,2]

CladT, a HE therapy, is approved in the United States for the treatment of people with RMS (PwRMS) and is known to preferentially reduce blood levels of B and T lymphocytes[3]

Switching rapidly from NTZ to CladT may provide sustained disease remission through reduction of peripherally sequestered autoreactive and encephalitogenic lymphocytes. At-home, short-course oral CladT may also be more convenient for patients than regular office/hospital NTZ infusions

METHODS

CLADRINA (NCT04178005) is an open-label, phase 4 study in PwRMS (N=40) who switched to CladT within 4 weeks of their last infusion with NTZ

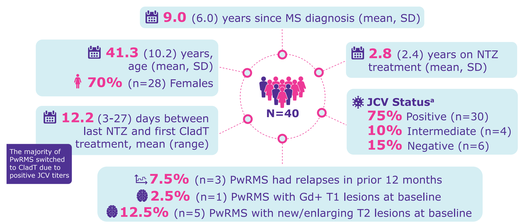
The primary outcome was change in CD3+ T lymphocytes and CD19+ B lymphocytes, from baseline to months 12 and 24 as assessed by flow cytometry

Annualized relapse rates (ARRs), Expanded Disability Status Scale (EDSS) scores, magnetic resonance imaging (MRI) outcomes, MSDA scores (Octave Bioscience [California, USA]), lymphocyte dynamics, and overall safety profile over 24 months are also reported

Please refer to the **Supplementary Figure 1** for CLADRINA study design and **Supplementary Figure 2** for more details on MSDA pathway categories and biomarkers.

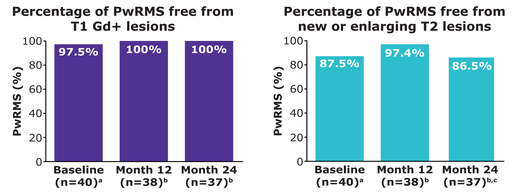
RESULTS

Figure 1. Baseline demographics and disease characteristics



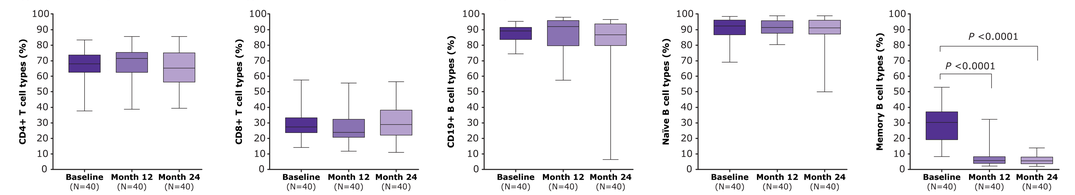
[a]Positive, JCV titer >0.40; Intermediate, JCV titer ≥0.20 to ≤0.40; Negative, JCV titer <0.20.
CladT, cladribine tablets; Gd+, gadolinium-enhanced; JCV, John Cunningham virus; MS, multiple sclerosis; NTZ, natalizumab; PwRMS, people with relapsing MS; SD, standard deviation.
Please refer to **Supplementary Table 1** for more details on baseline characteristics.

Figure 2. The percentage of PwRMS who were free of MRI activity remained stable over 24 months after switching from NTZ to CladT



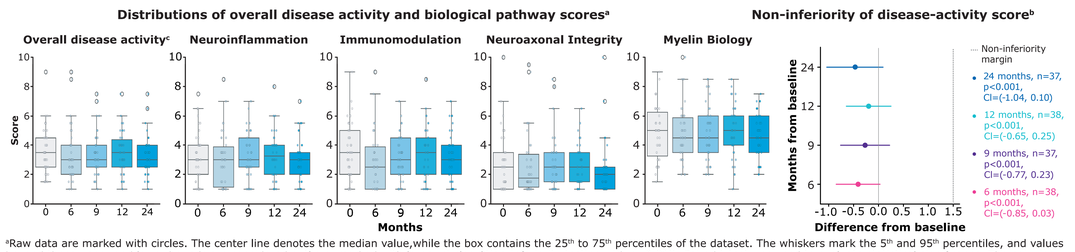
[a]Baseline MRI scan compared with previous year's scan. [b]n=2 patients withdrew from the study; and n=1 patient missed the 24 month MRI scan. [c]At Month 24, 5 patients had new/enlarging T2 lesions; two of these patients had 1 lesion each, 2 patients had 2 lesions each and 1 patient had 4 lesions.
CladT, cladribine tablets; Gd+, gadolinium-enhancing; MRI, magnetic resonance imaging; NTZ, natalizumab; PwRMS, people with relapsing multiple sclerosis.
Figure updated in poster after presentation at ACTRIMS 2025 (Updated: 21 March 2025).

Figure 3. CD4+ T cells, CD8+ T cells, CD19+ B cells, and naïve B cells remained stable, while memory B cells were significantly reduced through 24 months after switching to CladT



The central horizontal line represents the median value; Box represents the 25th-75th quartile; whiskers represent minimum and maximum values.
CladT, cladribine tablets; CD, cluster of differentiation. Please refer to **Supplementary Table 2** for information on median percentage change from baseline to months 12 and 24 in the various cell types

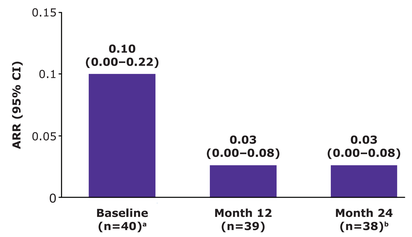
Figure 4. The MSDA score results were non-inferior vs. baseline over 24 months



[a]Raw data are marked with circles. The center line denotes the median value,while the box contains the 25th to 75th percentiles of the dataset. The whiskers mark the 5th and 95th percentiles, and values beyond these upper and lower bounds are considered outliers, marked with larger circles. [b]Non-inferiority testing with α=0.013; Paired t-test was used to evaluate statistical significance. The pairwise comparisons for the t-tests correspond to differences between follow up and baseline DA score. [c]Disease activity score thresholds; low: 1.0–4.0; moderate: 4.5–7.0; and high: 7.5–10.0.
CladT, cladribine tablets; CI, confidence interval; DMT, disease-modifying therapy; MSDA, Multiple Sclerosis Disease Activity; SD, standard deviation.

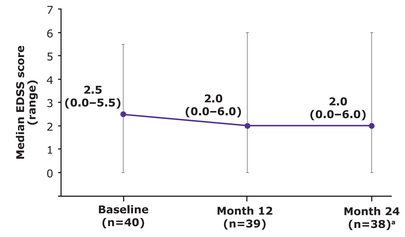
- 1.5 disease activity score units were utilized as the margin to establish non-inferiority of the overall disease activity score post DMT switch (MSDA analytical variability ±3 SD=1.5 disease activity score)

Figure 5. ARR remained stable over 24 months after switching from NTZ to CladT



[a]The ARR was calculated based on the number of relapses in the year prior to initiating CladT. [b]n=2 discontinued the study. ARR, annualized relapse rate; CladT, cladribine tablets; CI, confidence interval; NTZ, natalizumab.

Figure 6. EDSS scores remained stable over 24 months after switching from NTZ to CladT



[a]n=2 discontinued the study.
CladT, cladribine tablets; EDSS, Expanded Disability Status Scale; NTZ, natalizumab.

SAFETY

- Of the 40 PwRMS, 36 experienced an adverse event (AE) during the study. The most frequently reported study drug-related AEs were upper respiratory infection (12.5%), nausea (10%), and headache (7.5%)
- Three severe AEs were reported in PwRMS treated with CladT (breast cancer, parainfluenza, and traumatic pancreatitis [n=1 each])
- Two PwRMS discontinued the study due to AEs (shingles, n=1 [Year 1]; breast cancer, n=1 [prior to initiating CladT in Year 2]). No deaths were reported during the study

Please refer to **Supplementary Table 3** for more details on possible drug-related infection and other AEs over 24 months.

CladT was well tolerated by PwRMS who switched from NTZ to CladT over 24 months

All PwRMS (N=40) (number of events n=162)

Any AE	Any severe AE	AE leading to discontinuation	Serious infections	No serious opportunistic infections (including PML)
90% (n=36)	7.5% (n=3)	5% (n=2)	2.5% (n=1)	

AE, adverse event; CladT, cladribine tablets; NTZ, natalizumab; PML, progressive multifocal leukoencephalopathy; PwRMS, people with relapsing multiple sclerosis.

CONCLUSIONS

- **There was a significant reduction in memory B cells at Months 12 and 24 after switching to CladT, while CD19+ B cells, naïve B cells, CD4+ T cells, and CD8+ T cells remained stable**
- **The ARRs (Months 12, 24: 0.03; 0.03), EDSS scores, and T1 Gd+ MRI activity remained stable over 24 months after switching from NTZ (<1 month from last infusion) to CladT**
- **The overall disease activity score (MSDA) appeared either unchanged or lower, on an average after switching from NTZ to CladT at each time point (6, 9, 12 and 24 months) versus baseline which further supports continued disease stability**
- **No cases of PML or rebound disease activity were reported over 24 months after switching from NTZ to CladT**

SCAN FOR AFFILIATIONS, DISCLOSURES, AND SUPPLEMENTARY MATERIALS

References: 1. Shirani A, Stuve O. *Cold Spring Harb Perspect Med*. 2018;8:a029066.
2. O'Connor PW et al. *Neurology*. 2011;76:1858–1865.
3. Mavenclad. Prescribing information. EMD Serono, Inc; 2024.

Presented at ACTRIMS 2025 Forum | February 27–March 1 | West Palm Beach, FL, USA (Updated: 21 March 2025)

SUPPLEMENTARY MATERIAL

Supplementary Table 1. Baseline demographics and disease characteristics

Characteristics	N=40
Age in years, mean (SD)	41.3 (10.2)
Female, n (%)	28 (70.0)
Years since MS diagnosis, mean (SD)	9.0 (6.0)
Years on NTZ treatment, mean (SD)	2.8 (2.4)
JCV status, n (%)	40 (100)
Positive (titer >0.40)	30 (75)
Intermediate (titer ≥0.20 to ≤0.40)	4 (10)
Negative (titer <0.20)	6 (15)
Titer in JCV-positive PwRMS, mean (SD)	2.3 (0.9)
Time in days between last NTZ and first CladT treatment, mean (range)	12.2 (3–27)
PwRMS with relapses in prior 12 months, n (%)	3 (7.5)
Total no. of relapses in prior 12 months	4
PwRMS with Gd+ T1 lesions at baseline, n (%)	1 (2.5)
Total no. of Gd+ T1 lesions	1
PwRMS with new/enlarging T2 lesions at baseline, n (%)	5 (12.5)
Total no. of new/enlarging T2 lesions	15

CladT, cladribine tablets; Gd+, gadolinium-enhancing; JCV, John Cunningham virus; MS, multiple sclerosis; NTZ, natalizumab; PwRMS, people with relapsing multiple sclerosis; SD, standard deviation.

Supplementary Table 2. Median percentage change from baseline to months 12 and 24 in various cell types

Subtype	Baseline	Month 12		Month 24	
	Median (%)	Median (%)	Change from baseline	Median (%)	Change from baseline
CD4+ T cells	68.0 N=40	71.4 N=40	+3.4	65.2 N=40	−2.8
CD8+ T cells	27.4 N=40	23.8 N=40	−3.6	28.9 N=40	+1.5
CD19+ B cells	89.2 N=40	92.0 N=40	+2.8	86.7 N=40	−2.5
Naïve B cells	92.4 N=40	91.4 N=40	−1.0	91.2 N=40	−1.2
Memory B cells	30.3 N=40	5.7 N=40	−24.6	5.6 N=40	−24.7

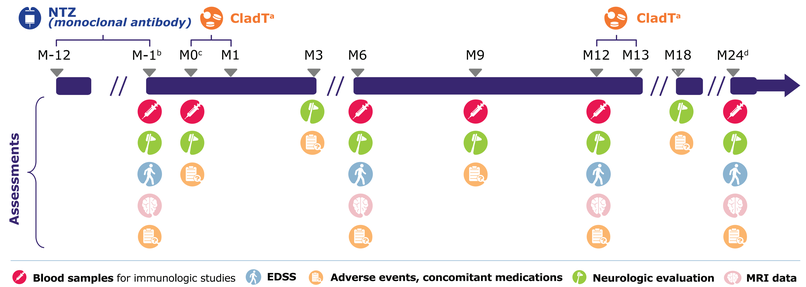
CladT, cladribine tablets; CD, cluster of differentiation.

Supplementary Table 3. Possible drug-related infections and other AEs over 24 months

AEs	N=40
Possible drug-related infections, PwRMS, n	
Upper respiratory infection	5
Thrush	2
COVID-19 infection	1
Gastrointestinal illness	1
Shingles	1
Vaginal yeast infection	1
Viral bronchitis	1
Possible drug-related other AEs, events, n	
Nausea	4
Headache	3
Fatigue	1
Loss of appetite	1
Vomiting	1

AE, adverse event; COVID-19, coronavirus disease 2019; PwRMS, people with relapsing multiple sclerosis.

Supplementary Figure 1. CLADRINA study design

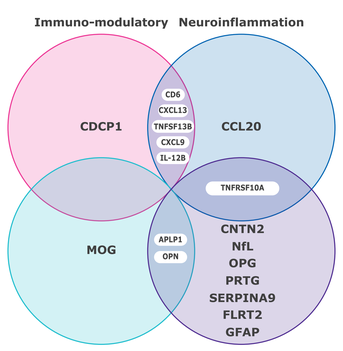


[a]CladT 10 mg tablets (3.5 mg/kg cumulative dose over 2 years) were administered per the USPI[1]; Year 2 treatment may be delayed up to 6 months to allow for lymphocyte recovery. [b]Screening. [c]Baseline (Day 1). [d]Follow-up can increase to up to 30 months depending on timing of Year 2 dose.

CladT, cladribine tablets; EDSS, Expanded Disability Status Scale; M, month; MRI, magnetic resonance imaging; MSDA, Multiple Sclerosis Disease Activity; USPI, United States Prescribing Information.

1. Mavenclad. Prescribing information. EMD Serono, Inc; 2024

Supplementary Figure 2. MSDA pathway categories and biomarkers



- The MSDA test measures 18 biomarkers to produce scores for four disease pathways. The individual biomarkers scores are then used to calculate an overall disease activity score[1,2]
- The pathways include immunomodulation, neuroinflammation, myelin biology and neuroaxonal integrity[1,2]
- The MSDA test has been both analytically and clinically validated relative to radiographic and clinical endpoints of disease activity[1,2]
- The MSDA test is scaled from 1.0–10.0 with intervals of 0.5 units. A score of 1.0–4.0 defines low activity, 4.5–7.0 indicates moderate activity, and 7.5–10.0 denotes high activity[1,2]
- The MSDA test was used to assess the association of protein biomarkers with stability after disease-modifying therapy switch using a non-inferiority test at 6, 9, 12, and 24 months relative to baseline

APLP1, amyloid beta precursor-like protein 1; CCL20, C-C motif chemokine ligand 20; CDCP1, CUB domain-containing protein 1; CNTN2, contactin 2; CXCL9, chemokine (C-X-C motif) ligand 9; CXCL13, chemokine (C-X-C motif) ligand 13; D6, cluster of differentiation 6; FLRT2, fibronectin leucine-rich repeat transmembrane protein; GFAP, glial fibrillary acidic protein; IL-12B, interleukin-12 subunit beta; MOG, myelin oligodendrocyte glycoprotein; MSDA, Multiple Sclerosis Disease Activity; NfL, neurofilament light chain; OPG, osteoprotegerin; OPN, osteopontin; PRTG, protogenin; SERPINA9, serpin family A member 9; TNFRSF10A, tumour necrosis factor receptor superfamily member 10A; TNFSF13B, tumour necrosis factor superfamily member 13B.

1. Chitnis T et al. *Clin Immunol.* 2023;253:109688; 2. Qureshi F et al. *Proteomics Clin Appl.* 2023;17(3):e2200018.

SUPPLEMENTARY MATERIAL

Author Affiliations

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Author Disclosures

PS has received research support from PSTP, CTM, PRC, the NMSS/IPMSA, PCORI, Genentech, Clene Nanomedicine, the NIH, and the DOD/CDMRP. He has received consulting fees from EMD Serono, Genentech, Horizon Therapeutics, and Bristol Myers Squibb.

AO has received speaking and consulting fees from Alexion, Biogen, Bristol Myers Squibb, EMD Serono, Roche Genentech, and Sanofi Genzyme and received research support from Alexion, Biogen, Novartis, EMD Serono, Roche Genentech, Sanofi Genzyme, and TG Therapeutics.

JK has received speaking and consulting fees from Abbvie, Allergan, Amgen, Biogen, Biohaven, Bristol Myers Squibb, EMD Serono, Horizon, Lilly, Lundbeck, Mallinckrodt, Sanofi-Genzyme, and Teva and participated in advisory boards for Genentech.

KB received research support from UCB and NeuroNEXT. He has served as an advisor to TG Therapeutics.

LT has received consulting fees from EMD Serono, Celgene. She is also a non-paid medical advisor for The MOG Project. She has also received paid support from MJH Life Sciences and NeurologyLive.

AS has received research funding from CMSC, Multiple Sclerosis Society of Canada, NMSS, and the US DOD and is a member of the editorial board for Neurology. She serves as a consultant for Gryphon Bio, LLC, Sora Neuroscience, and Abata Therapeutics. She has equity in Owl Therapeutics. She is a member of the DSMB for PREMOD2, CAVS-MS, and MARCH.

NM, and **RH** have nothing to disclose.

EE and **JK** are employees of EMD Serono, Boston, MA, USA.

FQ is an employee of Octave Bioscience, California, USA. **JE**, and **AG** are former employees of Octave Bioscience, California, USA.

OS serves on the editorial boards of Therapeutic Advances in Neurological Disorders, Expert Review of Clinical Immunology, and he is a section editor for Current Treatment Options in Neurology, has served on data monitoring committees for Genentech-Roche, and Novartis without monetary compensation, has advised EMD Serono, Novartis, and Octave Bioscience, receives grant support from EMD Serono, is a 2021 recipient of a Grant for Multiple Sclerosis Innovation (GMSI), the healthcare business of Merck KGaA Darmstadt, Germany, is funded by a Merit Review grant (federal award document number (FAIN) BX005664-01 from the United States (U.S.) Department of Veterans Affairs, Biomedical Laboratory Research and Development, is funded by RFA-2203-39314 (PI) and RFA-2203-39305 (co-PI) grants from the National Multiple Sclerosis Society (NMSS).

Acknowledgements

This work was sponsored by EMD Serono (CrossRef Funder ID: 10.13039/100004755). Medical writing support was provided by Ramya T of Merck Specialties Pvt. Ltd., Bengaluru, India, an affiliate of Merck KGaA Darmstadt, Germany.