Safety and Effectiveness of Cladribine Tablets after Treatment with Natalizumab (CLADRINA Trial) – 2-Year Results

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RESEARCH IN CONTEXT

The findings of the 2-year CLADRINA study suggest disease stability in people with relapsing multiple sclerosis (PwRMS) transitioning from natalizumab (NTZ) to cladribine tablets (CladT) and support the consideration of CladT as an effective and safe option after NTZ therapy.

OBJECTIVE

The CLADRINA study reports on the effectiveness, safety and MS Disease Activity score (MSDA) in PwRMS over 24-months after switching to CladT from NTZ within 1 month of their last infusion

INTRODUCTION

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

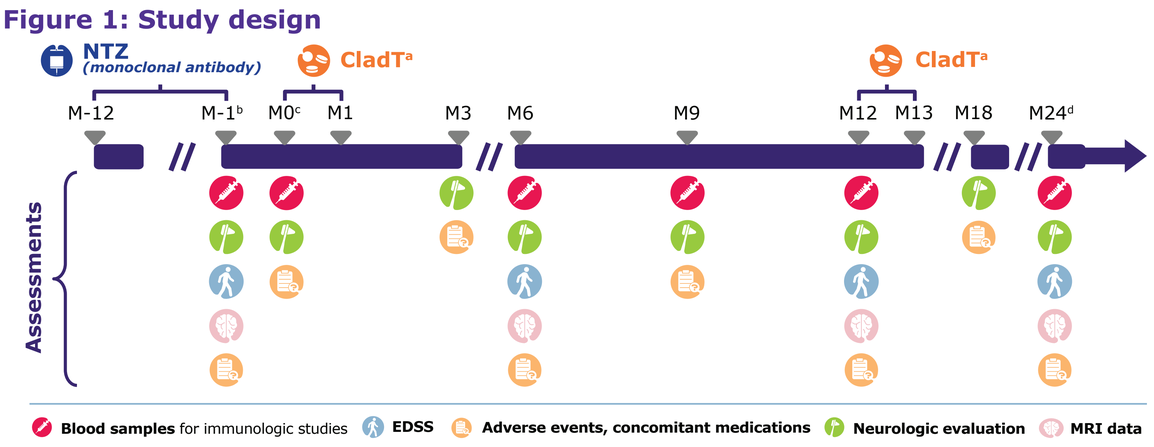
CladT, a HE therapy, is approved in the United States for the treatment of PwRMS and is known to preferentially reduce blood levels of B and T lymphocytes[3]

Switching rapidly from NTZ to CladT may be particularly advantageous in terms of sustained disease remission through the reduction of peripherally sequestered autoreactive and encephalitogenic lymphocytes.[3] Switching may also provide convenience of at home short-dose CladT vs monthly in office/hospital infusions of NTZ therapy

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
- Here we report the annualised relapse rates (ARRs), Expanded Disability Status Scale (EDSS) scores, magnetic resonance imaging (MRI) outcomes, MSDA scores (Octave Bioscience [California, USA]) and overall safety profile over 24 months
  - The MSDA score measures 18 biomarkers to produce scores for four disease pathways. The individual biomarkers and scores are then used to calculate an overall disease activity score[4,5]

Figure 1: Study design



[a]CladT 10 mg tablets (3.5 mg/kg cumulative dose over 2 years) were administered per the USPI[3] ; Year 2 treatment may be delayed up to 6 months to allow for lymphocyte recovery. [b]Screening. [c]Baseline (Day 1). [c]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; MSDA, Multiple Sclerosis Disease Activity; MRI, magnetic resonance imaging; NTZ, natalizumab; USPI, United States Prescribing Information.
Please refer to **Supplementary Figure 1** for more details on MSDA pathway categories and biomarkers.

RESULTS

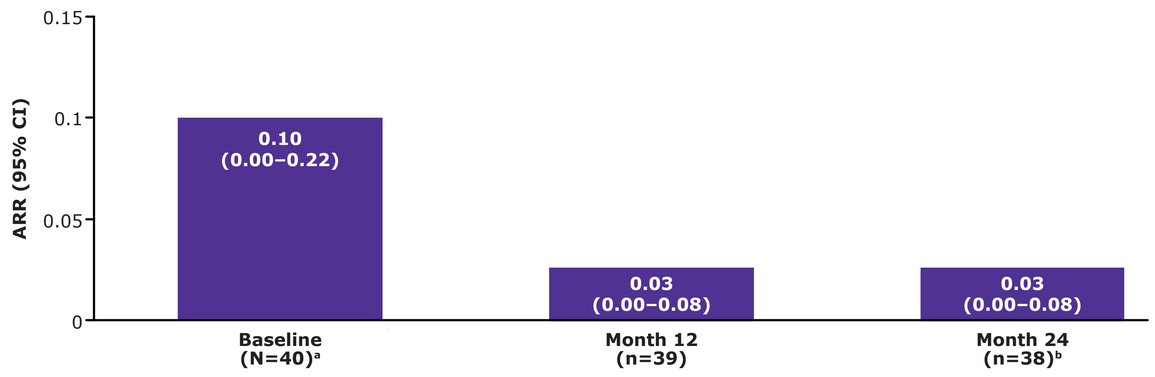
Table 1: Baseline demographics and disease characteristics

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; PwRMS, people with relapsing multiple sclerosis; NTZ, natalizumab; SD, standard deviation.

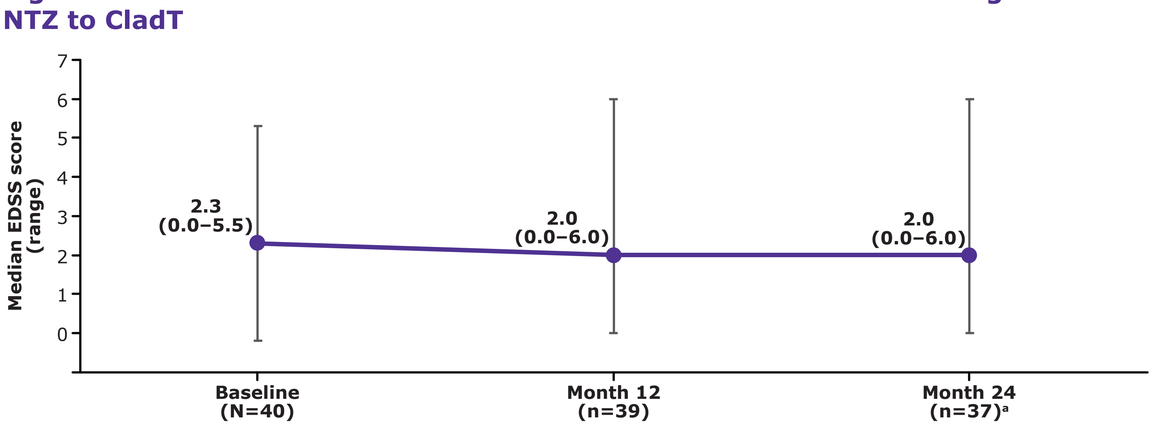
- The mean (range) time between NTZ discontinuation and CladT initiation was 12.2 (3–27) days
- The majority of PwRMS switched to CladT due to positive JCV titers

Figure 2: ARR remained stable over 24 months after switching from NTZ to CladT



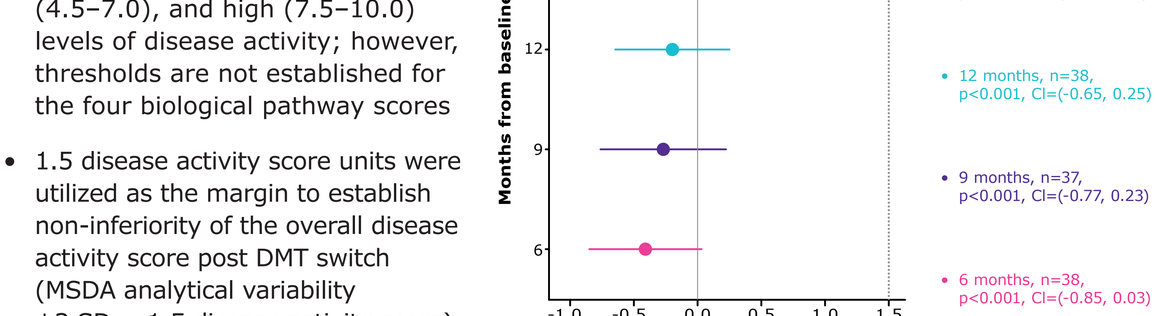
[a]The ARR was calculated based on the number of relapses in the year prior to initiating CladT. [b]n=2 discontinued the study.
ARR, annualised relapse rate; CladT, cladribine tablets; CI, confidence interval; NTZ, natalizmumab.

Figure 3: EDSS scores remained stable over 24 months after switching from NTZ to CladT



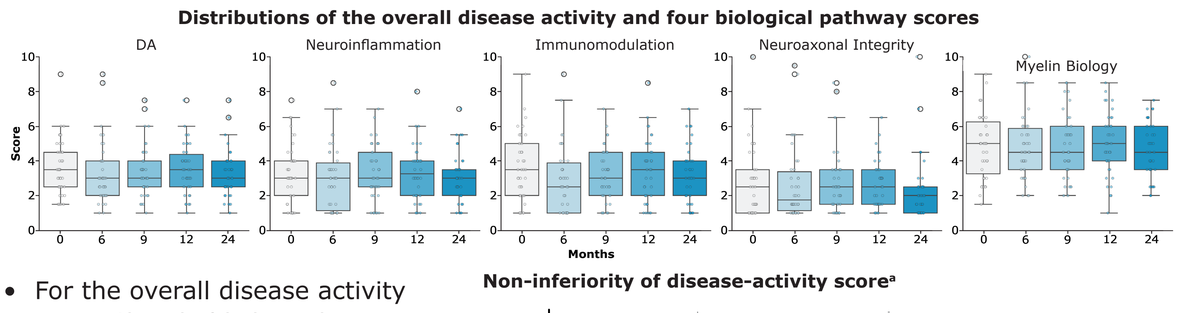
[a]n=2 discontinued the study; n=1 is yet to complete Month 24 visit.
CladT, cladribine tablets; EDSS, Expanded Disability Status Scale; NTZ, natalizmumab.

Figure 4: 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 discontinued the study; n=2 are yet to complete Month 24 visit.
CladT, cladribine tablets; Gd+, gadolinium-enhancing; HE, highly effective; MRI, magnetic resonance imaging; NTZ, natalizumab; PwRMS, people with relapsing multiple sclerosis.

Figure 5: The MSDA score results were non-inferior over 24 months



- For the overall disease activity score, thresholds have been established that correspond to low (1–4), moderate (4.5–7.0), and high (7.5–10.0) levels of disease activity; however, thresholds are not established for the four biological pathway scores
- 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)

Non-inferiority of disease-activity score[a]

[a]Non-inferiority testing with α=0.013; Paired t-tests used to evaluate statistical significance.
CladT, cladribine tablets; DMT, disease-modifying therapy; MSDA, Multiple Sclerosis Disease Activity; SD, standard deviation.

Table 2: CladT were well tolerated by PwRMS who switched from NTZ to CladT over 24 months

Characteristics	N=40
Any AE, events, n	162
Any AE, PwRMS, n (%)	36 (90.0)
AE leading to discontinuation, PwRMS, n (%)[a]	2 (5.0)
Death, PwRMS, n	0
Any severe AE, PwRMS, n (%)	3 (7.5%)
Serious infections, PwRMS, n (%)	1 (2.5)
Serious opportunistic infections (including PML), PwRMS, n (%)	0

[a]AE leading to treatment discontinuation: breast cancer (n=1); shingles (n=1).
AE, adverse event; CladT, cladribine tablets; NTZ, natalizmumab; PML, progressive multifocal leukoencephalopathy; PwRMS, people with relapsing multiple sclerosis.

- Of the 40 PwRMS, 36 experienced an adverse event (AE) during the study. The most commonly 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])

Please refer to **Supplementary Table 1** for more details on possible drug-related infection and other AEs over 24 months.

CONCLUSIONS

- **The ARRs (Months 12, 24: 0.03, 0.03), EDSS scores, and MRI activity remained stable over 24 months after switching from NTZ to CladT**
- **Overall disease activity score (MSDA) was not inferior (e.g. either unchanged or lower, or 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

Reference: 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; 4. Chitnis T et al. *Clin Immunol.* 2023;253:109688; 5. Qureshi F et al. *Proteomics Clin Appl.* 2023;17(3):e2200018.

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Supplementary Materials

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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 CELLO.

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

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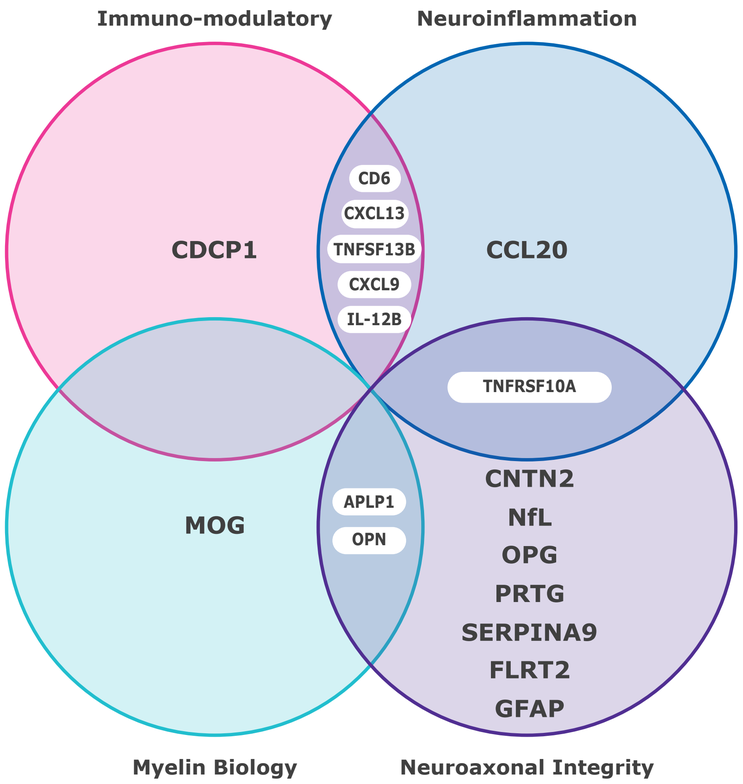
Supplementary Materials

Supplementary Figure 1: 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; D6, cluster of differentiation 6; 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; 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 Table 1: Possible drug-related infections and other AEs over 24 months

Characteristics	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.