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Safety and Effectiveness of Cladribine Tablets After Treatment With Natalizumab (CLADRINA) Trial – Interim Analysis

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CONCLUSIONS

- **After switching to cladribine tablets within 4 weeks of discontinuing natalizumab, annualized relapse rate (ARR), Expanded Disability Status Scale (EDSS), and magnetic resonance imaging (MRI) activity remained stable through 12 months**
- **No cases of progressive multifocal leukoencephalopathy (PML) or rebound disease activity have been reported to date**
- **A non-inferiority test was performed on the Multiple Sclerosis Disease Activity (MSDA) test results, and the overall disease activity score remained stable after switching from natalizumab to cladribine tablets at each time point (6, 9, and 12 months) versus baseline ($p<0.05$)**
- **This interim analysis supports the efficacy and safety of treatment with cladribine tablets within 4 weeks of discontinuing natalizumab**
- **Evaluation of immunological and clinical data is ongoing and may provide additional insight into the advantages of switching to cladribine tablets after natalizumab**

INTRODUCTION

- Natalizumab is highly effective in reducing multiple sclerosis (MS) disease activity but is associated with increased risk of developing PML and increased risk of MS rebound following treatment cessation[1,2]
- Data are needed on appropriate therapies (and timing) to follow natalizumab to prevent disease reactivation or rebound and induce prolonged disease remission following switches from natalizumab. Cladribine tablets 3.5 mg/kg are approved for treating forms of relapsing MS (RMS) in adults including relapsing-remitting MS (RRMS) and active secondary progressive MS (SPMS)[3]

OBJECTIVE

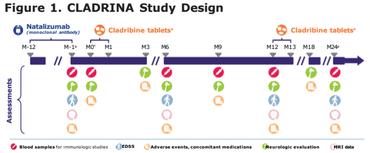
- **The CLADRINA Study is designed to generate real-world data regarding the safety and effectiveness of switching to cladribine tablets from natalizumab within 1 month post-infusion in patients with RMS**
- **This poster summarizes the 12-month interim analysis data of clinical biomarkers and safety for 40 enrolled patients; 38 of the 40 patients (95.0%) completed 12 months of follow-up. The primary outcome will be presented in forthcoming reports**

METHODS

Study Design

- CLADRINA is an open-label, phase 4 study in 40 participants with RMS reporting on effectiveness and safety outcomes in patients who switched from natalizumab to cladribine tablets (**Figure 1**)

Figure 1. CLADRINA Study Design



*Cladribine 10 mg tablets (3.5 mg/kg cumulative dose over 2 years) are administered per the USPI[3]; Year 2 treatment may be delayed up to 6 months to allow for lymphocyte recovery. †Screening. ‡Baseline (Day 1). §Follow-up can increase to up to 30 months depending on timing of Year 2 dose.
EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging.

Treatment

- All study participants will receive treatment with cladribine tablets (3.5 mg/kg cumulative dose over 2 years) according to the approved USPI.[3] Initiation of treatment with cladribine tablets is recommended to begin approximately 14 days after the last infusion of natalizumab, but a period of up to 1 month between natalizumab and cladribine tablets is allowed

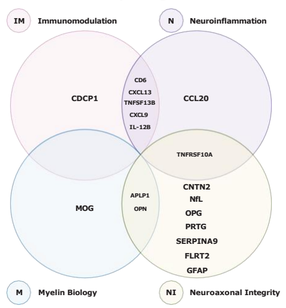
Study Endpoints

- This presentation reports clinical, radiological, and safety outcomes as well as Octave Bioscience's Multiple Sclerosis Disease Activity (MSDA) test through 12 months
- The primary outcome will be presented in future readouts

Octave Bioscience's MSDA Test

- The MSDA test measures 18 biomarkers to produce scores for 4 disease pathways. The individual biomarkers and scores are then used to calculate an overall disease activity score (**Figure 2**)
- Pathways include immunomodulation, neuroinflammation, myelin biology, and neuroaxonal integrity
- The MSDA test has been both analytically[4] and clinically[5] validated relative to radiographic and clinical endpoints of disease activity
- The MSDA test is scaled from 1-10 with 0.5 intervals. A score of 1.0-4.0 defines low activity, 4.5-7.0 indicates moderate activity, and 7.5-10 denotes high activity
- The MSDA test was used to assess the association of protein biomarkers with stability post disease-modifying therapy (DMT) switch using a non-inferiority test at months 6, 9, and 12 relative to baseline

Figure 2. MSDA Pathway Categories and Biomarkers



APLP1: Amyloid Beta Precursor Like Protein 1; CCL20: MIP-3 alpha; CD6: Cluster of Differentiation 6; CDCP1: CUB Domain-Containing Protein 1; CNTN2: Contactin 2; CXCL13: C-X-C Motif Chemokine Ligand 13; CXCL9: Monokine Induced by Gamma Interferon; FLRT2: Leucine-rich Repeat Transmembrane Protein; GFAP: Glial Fibrillary Acidic Protein; IL-12B: Interleukin 12B; MOG: Myelin-Oligodendrocyte Glycoprotein; NfL: Neurofilament Light; OPG: Osteoprotegerin; OPN: Osteopontin; PRTG: Protogenin; SERPINA9: Serpin Family A Member 9; TNFRSF10A: TRAIL1; TNFSF13B: B-cell activating factor.

RESULTS

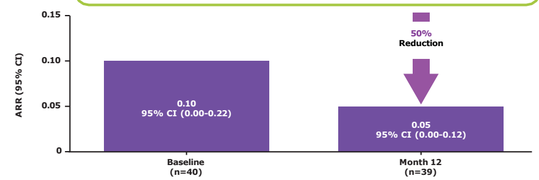
Table 1. Baseline Demographics and Disease Characteristics (N=40)

Patient Characteristics	
Age in years, mean (SD)	41.3 (10.2)
Female sex, n (%)	28 (70.0)
Years since MS diagnosis, mean (SD)	9.0 (6.0)
Years on natalizumab 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 patients, mean (SD)	2.3 (0.9)
Time in days between last natalizumab and first cladribine tablet treatment, mean (range)	12.2 (3-27)
No. of patients with relapses in prior 12 months, n (%)	3 (7.5)
Total no. of relapses in prior 12 months	4
No. of patients with Gd+ T1 lesions at baseline, n (%)	2 (5)
Total no. Gd+ T1 lesions in these 2 patients	11
No. of patients with new/enlarging T2 MRI lesions at baseline, n (%)	5 (12.5)
Total no. new/enlarging T2 lesions in these 5 patients	15

Gd+ T1, gadolinium-enhancing T1 lesion; JCV, John Cunningham virus; MRI, magnetic resonance imaging; MS, multiple sclerosis; No., Number.

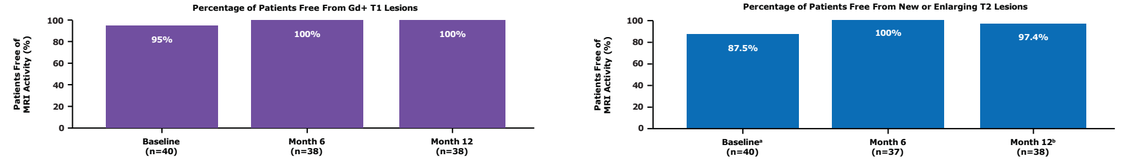
Figure 3. ARR at Baseline and 12 Months After Switching to Cladribine Tablets

Effectiveness
The ARR in the 12 months prior to switching to cladribine tablets was 0.10 (95% CI, 0.00-0.22). The ARR was 0.05 (95% CI, 0.00-0.12) 12 months after switching



ARR, annualized relapse rate.

Figure 4. Percentage of Patients Free of MRI Activity at Baseline, 6 Months, and 12 Months After Switching to Cladribine Tablets

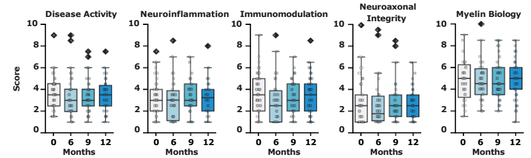


[a]Baseline scan compared with previous year's scan. [b]At 12 months, there were 3 new and enlarging T2-weighted lesions in 1 patient without clinical relapse.
Gd+ T1, gadolinium-enhancing T1 lesion; MRI, magnetic resonance imaging.

Octave MSDA Test Results

- For the overall disease activity score, thresholds have been established that correspond to low (1.0-4.0), moderate (4.5-7.0), and high (7.5-10.0) levels of disease activity; however, thresholds are not established for the 4 biological pathway scores (**Figure 5**)

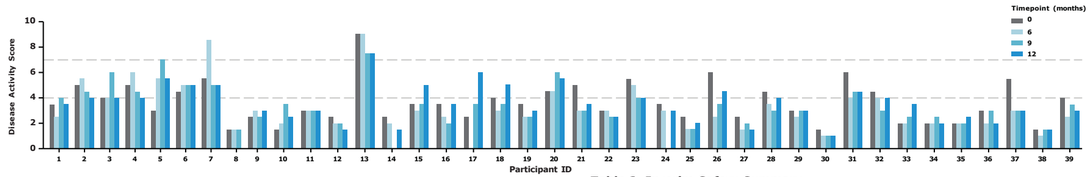
Figure 5. Distributions of Overall Disease Activity and 4 Biological Pathway Scores (n=39)



Raw data are marked with circles. The center line denotes the median value (50th percentile), 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 diamonds.

- **Overall Disease Activity Score Trajectories:** 39 patients completed 12-months of follow-up and samples from up to 4 time points were analyzed using the MSDA test (**Figure 7**)

Figure 7. Overall Disease Activity Score Trajectories for Each Individual Patient



- EDSS remained stable through 12 months. The median EDSS score in the 12 months prior to switching to cladribine tablets was 2.3 (range, 0.0-5.5) at baseline (n=40), 2.0 (range, 0.0-6.5) at 6 months (n=39), and 2.0 (range, 0.0-6.0) at 12 months (n=39)

Safety

- Cladribine tablets were well tolerated by patients after switching from natalizumab. The most common drug-related adverse events (AEs) were upper respiratory infection, nausea, and headache (**Table 2**)
- Four severe AEs were reported in 40 patients. The AEs were breast cancer (n=1), MS relapse (n=1), parainfluenza (n=1), and traumatic pancreatitis (n=1)

- **Non-inferiority of Disease Activity Score Differences From Baseline** 1.0 disease activity score unit was utilized as the margin to establish stability of the overall disease activity score post DMT switch (MSDA analytical variability ±2 SD = 1.0 disease activity) (**Figure 6**)

Figure 6. Non-inferiority of Disease Activity Score Differences From Baseline

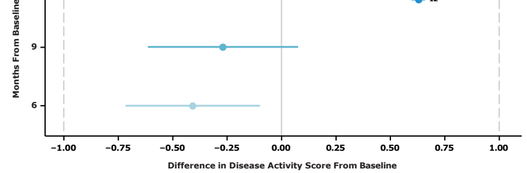


Table 2. Interim Safety Summary

Characteristic (N=40)	
Any AE — no. of events	162
Any AE — no. of patients (%)	36 (90.0)
AE leading to discontinuation — no. of patients (%)[a]	2 (5.0)
Death — no. of patients (%)	0
Any severe AE — no. of patients (%)	4 (10.0)
Serious infections — no. of patients (%)	1 (2.5)
Serious opportunistic infections — no. of patients	0
Possible drug-related infections — no. of events	
Upper respiratory infection	4
Thrush	2
Covid-19 infection	1
GI illness	1
Shingles	1
Vaginal yeast infection	1
Viral bronchitis	1
Possible drug-related other AEs — no. of events	
Nausea	4
Headache	3
Fatigue	1
Loss of appetite	1
Vomiting	1

[a]AEs leading to treatment discontinuation: breast cancer (n=1), shingles (n=1).
AE, adverse event; GI, gastrointestinal; No., number.

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 (cladribine) tablets [package insert]. EMD Serono, Inc.; 2022. **4.** Qureshi F, et al. *Proteomics Clin Appl*. 2023;17(3):e2200018. **5.** Chitnis T, et al. *Clin Immunol*. 2023;253:109688.

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