Poster # LB16

Cladribine Tablets After Treatment With Natalizumab (CLADRINA) Trial – Clinical Analysis

Peter Sguigna,[1] Annette Okai,[2] Jeffrey Kaplan,[3] Kyle Blackburn,[1] Lauren Tardo,[1] Lori Lebson,[4] Julie Korich,[4] Navid Manouchehri,[1] Rehana Hussain,[1] Amber Salter,[1] Olaf Stuve[1,5]

[1]University of Texas Southwestern Medical Center, Dallas, TX, USA; [2]North Texas Institute of Neurology & Headache, Plano, TX, USA; [3]Kansas City Multiple Sclerosis and Headache Center, Overland Park, KS, USA; [4]EMD Serono, Rockland, MA, USA; [5]VA North Texas Health Care System, Dallas VA Medical Center, Dallas, TX, USA

CONCLUSIONS

In this 12-month interim analysis of 40 patients, starting treatment with cladribine tablets within 28 days of natalizumab discontinuation was safe and effective. Rebound disease was not observed in these 40 patients through the first year of follow-up, and no cases of PML were reported.

BACKGROUND

- Natalizumab is highly effective in reducing MS disease activity but is associated with increased risk of developing PML and increased risk of MS disease rebound following treatment cessation[1,2]
- To prevent disease reactivation or rebound and induce prolonged disease remission following switches from natalizumab, data are needed on appropriate therapies (and timing) to follow natalizumab

OBJECTIVE

- **The purpose of the CLADRINA study is to generate hypotheses regarding the safety and effectiveness of cladribine tablets after switching from natalizumab in patients with RRMS or active SPMS**
- **This poster summarizes the 12-month interim data of secondary and exploratory outcomes for 40 enrolled patients. 33 out of 40 patients (82.5%) have completed 12 months. Of the 7 patients who did not complete 12 months, 2 patients discontinued, while the remaining 5 will reach 12 months of follow-up by July 2023. Primary outcomes will be reported in future reports**

METHODS

- CLADRINA is an open-label, phase 4 study in 40 participants with RRMS or active SPMS who meet the criteria for treatment with cladribine tablets as per the USPI

Treatment

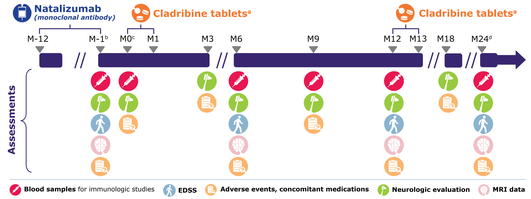
- All study participants will receive treatment with cladribine tablets (3.5 mg/kg cumulative dose over 2 years) according to the approved USPI.[3] Initiation of treatment with cladribine tablets is recommended to occur at approximately 14 days after the last infusion of natalizumab, but a period of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

Study Endpoints

- The primary endpoint is absolute and percentage change from baseline to 6, 9, 12, and 24 months of selected biomarkers in blood
- The secondary endpoints are ARR and percentage of patients experiencing a relapse over 12 and 24 months
- Exploratory measures include EDSS, MRI, and selected additional blood biomarkers
- Data available for this presentation include ARR, EDSS, MRI, and AEs to date; others will be presented in future communications

METHODS (cont.)

Figure 1. CLADRINA Study Design



[a]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. [b]Screening. [c]Baseline (Day 1). [d]Follow-up can increase to up to 30 months depending on timing of Year 2 dose.

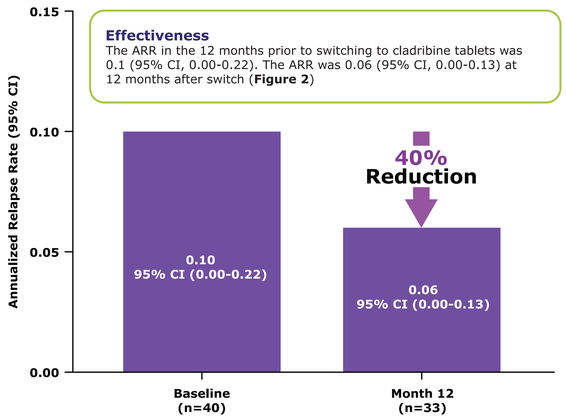
RESULTS

Table 1. Baseline Demographics and Disease Characteristics

Characteristic (N=40)	
Age, mean (SD)	41.3 (10.2)
Female sex, n (%)	28 (70.0)
Years since MS diagnosis, mean (SD)	8.7 (6.0)
Years on natalizumab treatment, mean (SD)	2.8 (2.2)
JCV status, n (%)	40 (100)
Positive (titer >0.40)	31 (77.5)
Intermediate (titer ≥0.20 to ≤0.40)	3 (7.5)
Negative (titer <0.20)	6 (15)
Titer range in JCV-positive patients, mean (SD)	2.2 (0.9)
No. of relapses in prior 12 months	4
Time in days between last natalizumab and first cladribine tablet treatment, mean (range)	12.18 (range 3-27)
No. of patients with Gd+ T1 lesions at baseline, n (%)	2 (0.05%)
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

RESULTS (cont.)

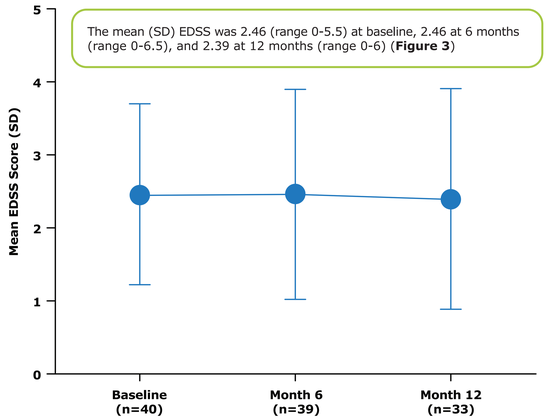
Figure 2. ARR at Baseline and 12 Months After Switching to Cladribine



Effectiveness

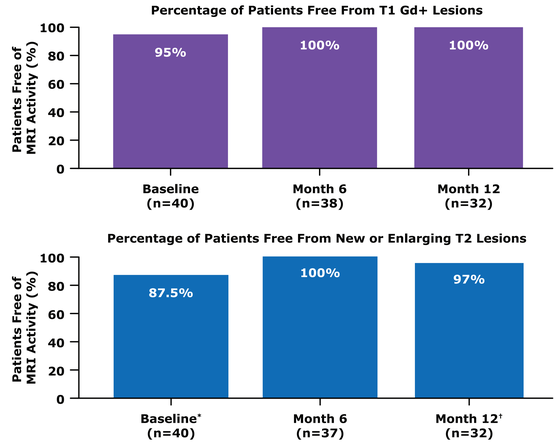
The ARR in the 12 months prior to switching to cladribine tablets was 0.1 (95% CI, 0.00-0.22). The ARR was 0.06 (95% CI, 0.00-0.13) at 12 months after switch (**Figure 2**)

Figure 3. Mean (SD) EDSS at Baseline, 6 Months, and 12 Months After Switching to Cladribine



The mean (SD) EDSS was 2.46 (range 0-5.5) at baseline, 2.46 at 6 months (range 0-6.5), and 2.39 at 12 months (range 0-6) (**Figure 3**)

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



*Baseline scan compared with previous year's scan.
†At 12 months, there were 3 new and enlarging T2-weighted lesions in 1 patient without clinical relapse.

Safety

- Cladribine tablets were well tolerated after switching from natalizumab, with COVID-19, nausea, and headache among the most common AEs
- The most common drug-related AEs were upper respiratory infection, nausea, and headache (**Table 2**)
- A single event was observed for the following drug-related AEs: COVID-19 infection, fatigue, loss of appetite, shingles, vaginal yeast infection, and vomiting

Table 2. Interim Safety Summary

Characteristic (N=40)	
Any AE — no. of events	141
Any AE — no. of patients (%)	36 (90.0)
AE leading to discontinuation of cladribine tablet — no. of patients (%)	2 (5.0)
Death — no. of patients (%)	0
Any severe AE — no. of patients (%)	4 (10.0)
Serious infections — no. of patients (%)	0
Specific drug-related AE — no. of events	
Upper respiratory infection	4
Nausea	4
Headache	3
Thrush	2

Abbreviations: AE, adverse event; **ARR,** annualized relapse rate; **COVID-19,** coronavirus disease 2019; **EDSS,** Expanded Disability Status Scale; **Gd+,** gadolinium-enhancing; **JCV,** John Cunningham virus; **MRI,** magnetic resonance imaging; **MS,** multiple sclerosis; **PML,** progressive multifocal leukoencephalopathy; **RRMS,** relapsing-remitting multiple sclerosis; **SPMS,** secondary progressive multiple sclerosis; **USPI,** United States Prescribing Information.

References: 1. Shirani A, and Stuve O. *Cold Spring Harb Perspect Med*. 2018;8:a029066. **2.** O'Connor PW, et al. *Neurology*. 2011;76:1858–1865. **3.** Mavenclad [package insert]. EMD Serono, Inc., Rockland, MA, USA; 2019.

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