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Self-Reported Adherence and Safety of Cladribine Tablets in Patients With Relapsing Multiple Sclerosis After Suboptimal Response to Prior Oral or Infusion Disease-Modifying Therapy: 6-Month Interim Analysis From the US-Based Phase 4 MASTER-2 Study

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CONCLUSIONS

- **This 6-month interim analysis showed stable EDSS scores, high self-reported treatment adherence, high treatment satisfaction and favorable tolerability with no new or unexpected safety findings with cladribine tablets among patients with RMS after switching from oral or infusion DMTs**
- **Results from the MASTER-2 study may help inform treatment decisions in real-world clinical practice**

INTRODUCTION

- MS is a chronic neurodegenerative autoimmune disease of the central nervous system characterized by gliosis, inflammation, and demyelination[1,2]
- Cladribine tablets (3.5 mg/kg cumulative dose over 2 years) are approved for treating forms of RMS in adults including RRMS and active SPMS[3]
- Real-world data on the effectiveness, adherence, and safety of cladribine tablets in patients switching from oral or infusion DMTs are limited
- This observational study provides 6-month efficacy, adherence, treatment satisfaction, and safety analysis of cladribine tablets in patients with RRMS or active SPMS with prior suboptimal response to an oral or infusion DMT in a real-world setting

OBJECTIVE

- **To evaluate the patient-reported treatment adherence and safety of cladribine tablets in those with RMS who had a suboptimal response[a] to an oral or infusion DMT in a real-world setting**

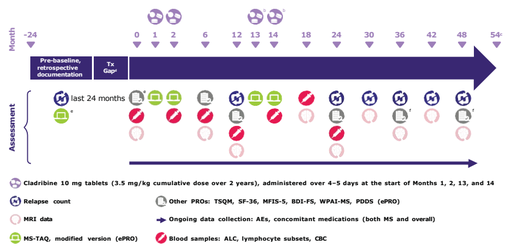
[a]Suboptimal as per protocol: lack of effectiveness, intolerability, poor adherence.

METHODS

Study Design

- MASTER-2 (NCT03933202) is an ongoing, observational, single-arm, 54-month, phase 4, US-based study (**Figure 1**)
- These analyses were conducted with data collected up to May 8, 2023

Figure 1. MASTER-2 Study Design[a]



[a]Since the publication of the study design,[4] the study duration has been extended to 54 months from 30 months to further collect data on safety, relapse, MRI, and PDDS. [b]Treatment in the second year may be delayed for up to 6 months for some patients, according to ALC. This is accounted for in the study duration. [c]If Year 2 treatment is delayed, follow-up may continue up to 54 months. [d]Duration between stopping previous DMTs and starting cladribine tablets was variable and at the discretion of the treating physician. [e]First assessment is for prior DMT. [f]PDDS only.

Eligibility Criteria

- Patients aged ≥18 years with RRMS or active SPMS treated with ≥1 course of cladribine tablets who switched after a suboptimal response to an oral or infusion DMT
- All patients are required to meet the United States Prescribing Information criteria for treatment with cladribine tablets

Study Endpoints

- The primary endpoint of this study is 24-month ARR after initiating treatment with cladribine tablets (this will be reported in future publications)
- Key secondary endpoints include EDSS score, adherence as assessed by the MS-TAQ, and safety

Statistical Analysis

- The 6-month interim analysis is based on baseline and 6-month data
- Population estimates of the ARR, its corresponding 95% CI, and descriptive statistics were based on the average of patients' ARR values. The ARR over 6 months for a patient is calculated as the patient's number of relapses per routine clinical practice divided by the patient's number of days on study, multiplied by 365.25
- Descriptive statistics are shown for EDSS, MS-TAQ, and baseline characteristics
- The most recent prior DMT was examined
- Serious TEAEs, discontinuations due to TEAEs, the most commonly reported TEAEs ≥4%, and lymphopenia are shown

RESULTS

Baseline Demographics and Disease Characteristics

- A total of 187 patients with RMS who switched to cladribine tablets after a suboptimal response to an oral (n=102) or infusion (n=85) DMT were included in this analysis (**Table 1**). A subgroup of patients who switched from ocrelizumab to cladribine tablets (n=51) was also analyzed
  - The mean (SD) overall ARRs 24 months prior to the study were 0.18 (0.29) and 0.13 (0.25) for patients who switched from oral and infusion DMTs, respectively
- The mean (SD) number of combined unique lesions at baseline were 3.9 (9.28) and 10.2 (12.67), respectively
- For the majority of patients, baseline absolute lymphocyte count levels were within normal ranges (76.5% and 82.4% of patients, respectively)

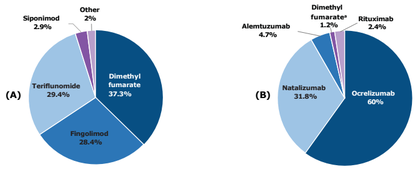
Table 1. Baseline Demographics and Disease Characteristics

Characteristics	Cladribine tablets 3.5 mg/kg (N=187)	
	Switch from oral DMT (n=102)	Switch from infusion DMT (n=85)
Female, n (%)	84 (82.4)	57 (67.1)
Age, years		
Mean (SD)	50 (10.8)	48 (12.6)
Min, max	19, 74	21, 70
Race, n (%)		
White	84 (82.4)	68 (80.0)
Black/African American	13 (12.7)	6 (7.1)
Asian	1 (1.0)	2 (2.4)
Other	4 (3.9)	6 (7.1)
Multiple	0	3 (3.5)
Diagnosis, n (%)		
RRMS	96 (94.1)	75 (88.2)
Active SPMS	5 (4.9)	10 (11.8)
Missing	1 (1.0)	0
Years elapsed since diagnosis, mean (SD)	12 (7.24)	13.5 (9.61)
Relapse in prior 24 months, n (%)		
0	63 (61.8)	55 (64.7)
1	25 (24.5)	15 (17.6)
2	2 (2.0)	2 (2.4)
3	1 (1.0)	0
≥4	0	0
ARR in prior 24 months, mean (SD)	0.18 (0.292)	0.13 (0.252)
Number of MRI lesions, mean (SD)		
T1 Gd+ lesions	0.3 (0.66)	0
New T2 lesions	0.9 (1.30)	0.9 (4.17)
Combined unique lesions	3.9 (9.28)	10.2 (12.67)
ALC (10^9/L), median (Q1; Q3)	1.4 (0.9; 2.0)	1.8 (1.4; 2.5)
ALC (10^9/L), n (%)		
Below lower limit of normal	1 (1.0)	1 (1.2)
Within normal range	78 (76.5)	70 (82.4)
Above upper limit of normal	1 (1.0)	1 (1.2)
Missing	22 (21.6)	13 (15.3)

Most Recent Prior DMT

- The most common prior oral DMTs used were dimethyl fumarate (37.3%, n=38/102), teriflunomide (29.4%, n=30/102), and fingolimod (28.4%, n=29/102) (**Figure 2**)
- The most common prior infusion DMTs used were ocrelizumab (60.0%, n=51/85) and natalizumab (31.8%, n=27/85)

Figure 2. (A) Common Prior Oral (n=102) and (B) Prior Infusion DMTs Used (n=85)



[a]Critical protocol deviation; 1 prior dimethyl fumarate incorrectly grouped with infusions.

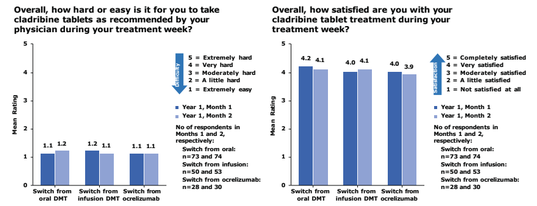
MS-TAQ for Cladribine Tablets

Adherence Rates

- Among MS-TAQ respondents, self-reported adherence rates for the full first year treatment course were high at ≥97.3% (n=72/74) for patients with prior oral DMTs and 100% (n=53/53) for patients with prior infusion DMTs, including ocrelizumab (n=30/30) (**Figure 3**)
- Among MS-TAQ respondents, high self-reported cladribine treatment satisfaction and favorable tolerability were reported for the full first year treatment course with a mean score ≥3.9

Patient Satisfaction

Figure 3. MS-TAQ for Cladribine Tablets



EDSS for Cladribine Tablets

- Overall, at 6 months following cladribine tablet initiation, median (Q1; Q3) EDSS scores remained stable at 3.0 (2.0; 5.5) for those who completed the EDSS assessment (n=34 [18.2%]) (**Table 2**)

Table 2. EDSS Score at 6 Months Following Cladribine Tablet Initiation

EDSS Score	Cladribine tablets 3.5 mg/kg							
	Overall (N=187)		Switch from oral DMT (n=102)		Switch from infusion DMT (n=85)		Switch from ocrelizumab (n=51)	
	Baseline	Month 6	Baseline	Month 6	Baseline	Month 6	Baseline	Month 6
Observed values								
n (%)	60 (32.1)	34 (18.2)	33 (32.4)	19 (18.6)	27 (31.8)	15 (17.6)	17 (34.7)	11 (22.4)
Median (Q1;Q3)	3.5 (1.8; 5.8)	3.0 (2.0; 5.5)	3.0 (1.5; 4.0)	3.0 (1.5; 3.5)	3.5 (2.5; 6.5)	3.5 (2.0; 6.5)	4.0 (2.5; 6.5)	3.5 (2.0; 6.0)

Safety

- Overall, 10.7% (n=20/187) of patients experienced serious TEAEs, and 4.8% (n=9/187) of patients discontinued due to TEAEs during the observation period
- The most common TEAEs (≥4% of patients) were fatigue (9.1%) and COVID-19 (6.4%) (**Table 3**)
- At 6 months, grade 3 lymphopenia was reported in 4.9% and 4.7% of patients, and grade 4 lymphopenia was reported in 2.0% and 0% of patients who switched from oral and infusion DMTs, respectively

Table 3. TEAEs (24-Month Treatment Period) in Patients Who Switched From an Oral or Infusion DMT to Cladribine Tablets

TEAEs	Cladribine tablets 3.5 mg/kg			
	Overall (N=187)	Switch from oral DMT (n=102)	Switch from infusion DMT (n=85)	Switch from ocrelizumab (n=51)
Any TEAE, n (%)	96 (51.3)	58 (56.9)	38 (44.7)	19 (37.3)
Severe	17 (9.1)	10 (9.8)	7 (8.2)	3 (5.9)
Moderate	54 (28.9)	29 (28.4)	25 (29.4)	15 (29.4)
Mild	78 (41.7)	48 (47.1)	30 (35.3)	15 (29.4)
Any serious TEAE, n (%)	20 (10.7)[a]	10 (9.8)	10 (11.8)	8 (15.7)
TEAEs leading to permanent discontinuation, n (%)	9 (4.8)[b]	9 (8.8)[b]	0	0
TEAEs leading to death, n (%)	1 (0.5)[c]	1 (1.0)[c]	0	0

[a]AEs unrelated to study treatment: fall or head injury (n=1); acute myocardial infarction (n=1); cerebrovascular accident (n=1); pyelonephritis, sepsis, and ureterolithiasis (n=1); sarcoma (n=1); pyelonephritis, ureterolithiasis, urosepsis, and clostridium difficile (n=1); breast cancer (n=1); breast cancer stage 1 (n=1); pregnancy (n=1); acute kidney injury (n=1), seizure like activity (n=1), breast cellulitis (n=1); laryngeal cancer (n=1); heavy menstrual bleeding (n=1); lung neoplasm malignant (n=1); hyponatremia, trigeminal neuralgia, and COVID-19 (n=1); optic neuritis (n=1); ureterolithiasis, urinary tract infection, and urinary tract obstruction (n=1). AEs related to study treatment: pyrexia and seizure (n=1); lymphocyte count decrease (n=1). [b]Discontinued due to lymphopenia (n=4); diarrhea (n=1); fatigue, headache, and rash (n=1); neutropenia (n=1); rash pruritic (n=1); lymphocyte count decreased (n=1). [c]59-year-old patient; AE was "event unrelated to study treatment: malignant neoplasm of lung" with the PT "lung neoplasm malignant."

Abbreviations: AE, adverse event; **ALC,** absolute lymphocyte count; **ARR,** annualized relapse rates; **BDI-FS,** Beck-Depression Inventory – Fast Screen; **CBC,** complete blood count; **DMT,** disease-modifying therapy; **ePRO,** electronic PRO; **EDSS,** Expanded Disability Status Scale; **Gd+,** gadolinium-enhancing; **MFIS-5,** Modified Fatigue Impact Scale – 5-item version; **MRI,** magnetic resonance imaging; **MS,** multiple sclerosis; **MS-TAQ,** MS Treatment Adherence Questionnaire; **PDDS,** Patient Determined Disease Steps; **PRO,** patient-reported outcome; **RRMS,** relapsing-remitting multiple sclerosis; **SF-36,** 36-Item Short Form Health Survey; **SPMS,** secondary progressive multiple sclerosis; **TEAEs,** treatment-emergent adverse events; **TSQM,** 14-Item Treatment Satisfaction Questionnaire for Medication; **Tx,** treatment; **WPAI-MS,** Work Productivity Activity Impairment – MS.

References: 1. Giovannoni G, Mathews J. *Neurol Ther.* 2022;11(2):571-95. **2.** Kamma E, et al. *J Neuroinflammation.* 2022;19(1):45. **3.** MAVENCLAD (cladribine) tablets [package insert]. EMD Serono, Inc.; 2022. **4.** Miravalle AA, et al. *Neurodegener Dis Manag.* 2021;11(2):99–111.

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