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Real-World Effectiveness and Safety of Cladribine Tablets in Patients with Relapsing MS after Suboptimal Response to Prior Oral or Infusion Disease-Modifying Therapy: 12-Month Interim Analysis from the US-Based Phase 4 MASTER-2 Study

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RESEARCH IN CONTEXT

1. **This interim analysis from the ongoing MASTER-2 study provides evidence for the use of cladribine tablets (CladT) in patients switching from oral or infusion disease-modifying therapies (DMTs).**
2. **In the 12 months after switching to CladT, the annualized relapse rate (ARR) was low at 0.04 and the Patient Determined Disease Steps (PDDS) score remained numerically lower than baseline. Treatment adherence and satisfaction were high with no new or unexpected safety signals.**

OBJECTIVE

To evaluate the 12-month effectiveness, safety, and treatment adherence of CladT in PwRMS enrolled in MASTER-2

INTRODUCTION

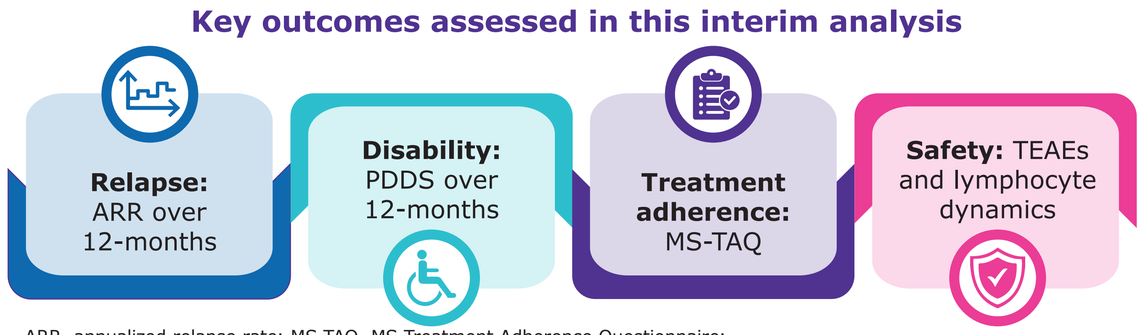
- CladT (3.5 mg/kg cumulative dose over 2 years) are approved in the United States for the treatment of people with relapsing multiple sclerosis (PwRMS)[1]
- Real-world effectiveness and safety data of CladT in US patients switching from DMTs are limited
- The 6-month data from the ongoing phase 4 MASTER-2 study (NCT03933202) suggested stable disability outcomes, no new or unexpected safety signals and high treatment adherence in PwRMS who switched from oral or infusion DMTs to CladT[2]

METHODS

- MASTER-2 (NCT03933202) is an ongoing, observational, single-arm, 24-month, phase 4, US-based study
- PwRMS who switched to CladT after a suboptimal response[a] to an oral or infusion disease-modifying therapy (DMT) were included in this analysis
- Interim analysis at 12 months, data cut off February 12, 2024

[a]Suboptimal as per protocol: lack of effectiveness, intolerability, poor adherence.
(Please refer to **Supplementary Figure 1** for more details on the study design)

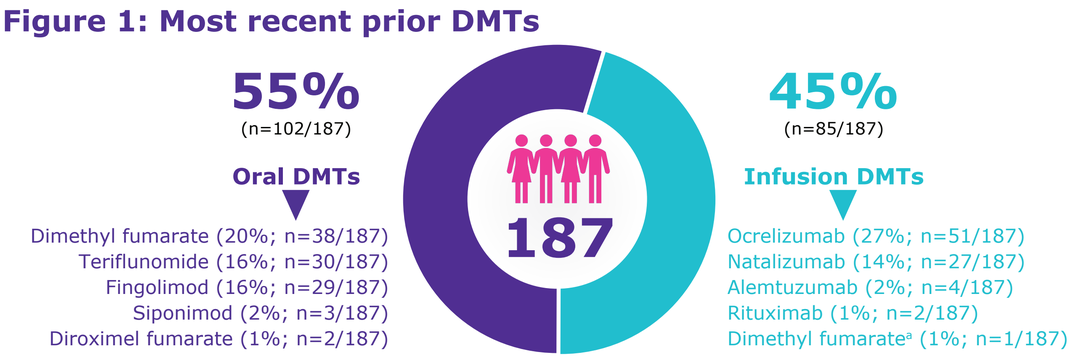
Key outcomes assessed in this interim analysis



ARR, annualized relapse rate; MS-TAQ, MS Treatment Adherence Questionnaire; PDDS, Patient Determined Disease Steps; TEAE, treatment-emergent adverse event.

RESULTS

Figure 1: Most recent prior DMTs



[a]Critical protocol deviation; 1 prior dimethyl fumarate incorrectly grouped with infusions. DMT, disease-modifying therapy.

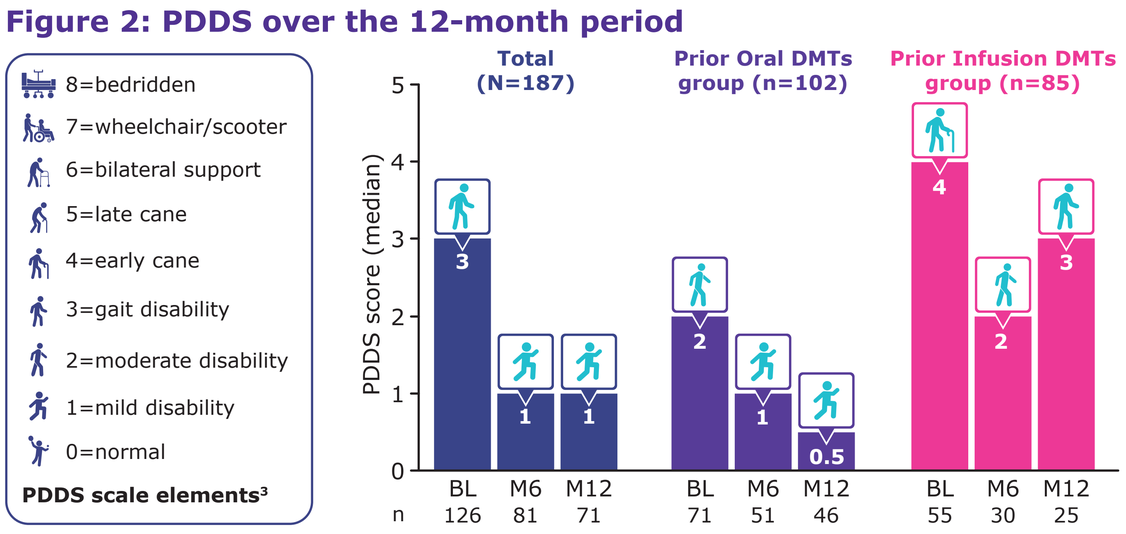
Table 1: ARR over the 12-month period

	CladT 3.5 mg/kg (N=187)		
	Total (N=187)	Prior Oral DMTs group (n=102)	Prior Infusion DMTs group (n=85)
ARR (previous 24-months or since MS diagnosis*) prior to switch to CladT	0.17±0.303	0.19±0.323	0.16±0.277
ARR over the 12-month post switch to CladT	0.04±0.201	0.04±0.197	0.04±0.206

Data are presented as mean±SD. *Previous 24-months (MS diagnosis ≥ 24 months) or since MS diagnosis (MS diagnosis <24 months).
ARR, annualized relapse rate; SD, standard deviation; DMT, disease-modifying therapy.

A total of 6 patients experienced relapses (one each) over the 12-month period (n=6; 3 in the prior oral and 3 in the prior infusion DMTs subgroups)

Figure 2: PDDS over the 12-month period



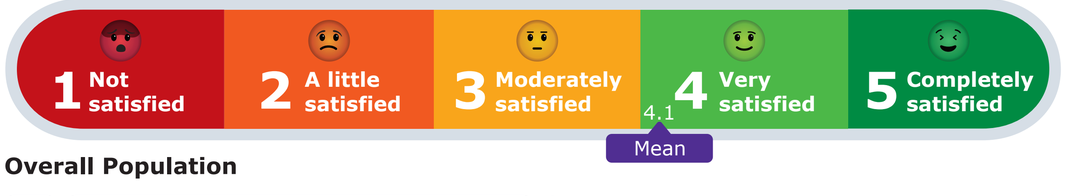
The median PDDS scores did not increase over the 12-month study period

BL, baseline; DMT, disease-modifying therapy; M6, month 6, M12, month 12; PDDS, Patient Determined Disease Steps.

Figure 3: Self reported adherence and treatment satisfaction: MS-TAQ

- Patients with available MS-TAQ scores: Month 1 (n=123) and Month 2 (n=127)

A. Overall, how hard or easy do you feel it is to take CladT as recommended by your physician during your treatment week?



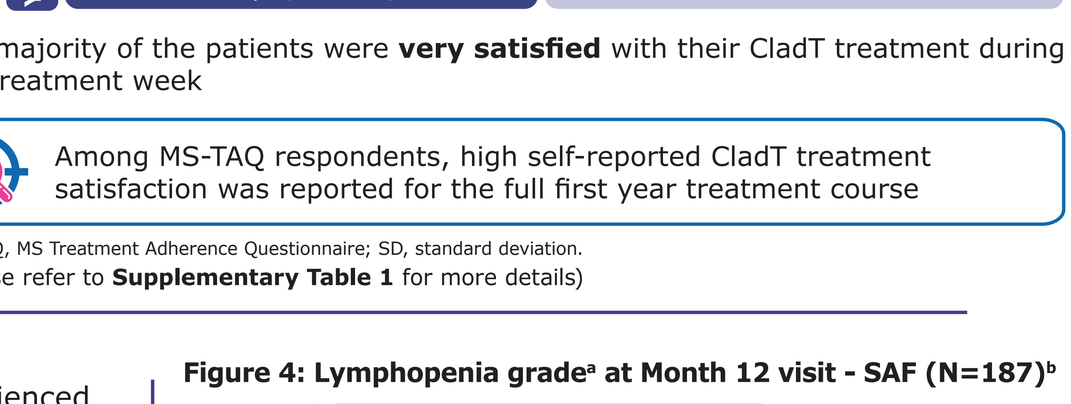
Overall Population

Year 1	Month 1; n/N=123/187	Mean±SD 1.1±0.39
	Month 2; n/N=127/187	Mean±SD 1.1±0.42

The majority of patients found it **extremely easy** to take CladT as recommended by their physician

Among MS-TAQ respondents, self-reported adherence to the full first year course CladT treatment was very high (99.2% for month 1 and 98.4% for month 2 treatment)

B. Overall, how satisfied are you with your CladT treatment during your treatment week?



Overall Population

Year 1	Month 1; n/N=123/187	Mean±SD 4.2±0.83
	Month 2; n/N=127/187	Mean±SD 4.1±0.92

The majority of the patients were **very satisfied** with their CladT treatment during the treatment week

Among MS-TAQ respondents, high self-reported CladT treatment satisfaction was reported for the full first year treatment course

MS-TAQ, MS Treatment Adherence Questionnaire; SD, standard deviation.
(Please refer to **Supplementary Table 1** for more details)

Safety overview

During the 12-month observation period, 54.5% (102/187) patients experienced TEAEs and most were mild or moderate in severity

The most common TEAEs were

- **Fatigue** 7.5% (n=14)
- **COVID-19** 7.0% (n=13)

10.2% (19/187) of patients experienced serious TEAEs

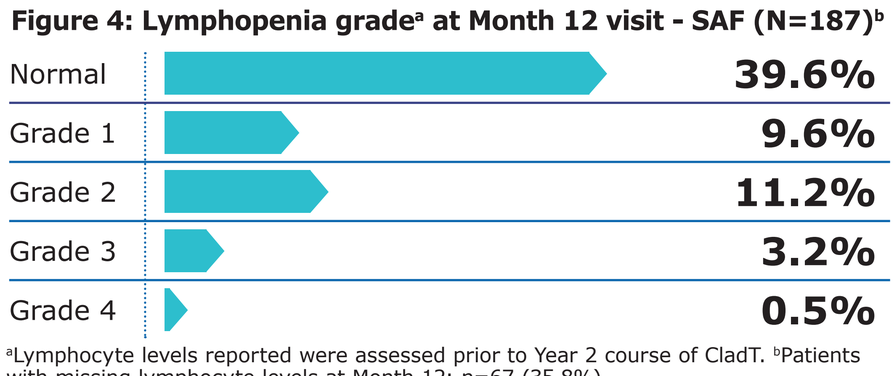
Notable serious TEAEs were lymphocyte count decrease, seizure like-activity and pyrexia (n=1 each)

4.8% (9/187) of patients permanently discontinued treatment due to TEAEs

No new or unexpected safety signals were identified during the study period

COVID-19, corona virus disease 2019; TEAE, treatment-emergent adverse event.

Figure 4: Lymphopenia grade[a] at Month 12 visit - SAF (N=187)[b]



[a]Lymphocyte levels reported were assessed prior to Year 2 course of CladT. [b]Patients with missing lymphocyte levels at Month 12: n=67 (35.8%).
Absolute lymphocyte count levels (cells/10^3mL): Normal, 1000 to 4800; Grade 1 lymphopenia, 800 to <1000; Grade 2 lymphopenia, 500 to <800; Grade 3 lymphopenia, 200 to <500; Grade 4 lymphopenia, <200.
SAF, safety analysis set.
(Please refer to **Supplementary Table 2** and **Figure 2** for more details)

CONCLUSIONS

- **This 12-month interim analysis supports continued real-world effectiveness (ARR = 0.04), safety, and high self-reported treatment adherence and satisfaction of CladT in PwRMS who transitioned to CladT after suboptimal response to other oral or infusion DMTs in a real-world setting**
- **Results from the MASTER-2 study may help inform treatment decisions in real-world clinical practice**

SCAN FOR AFFILIATIONS, DISCLOSURES AND SUPPLEMENTARY MATERIALS

References: 1. MAVENCLAD (cladribine) tablets [package insert]. EMD Serono, Inc.; 2024; 2. Bass A, et al. *ACTRIMS* 2024, P493; 3. Fox RJ, et al. *Int J MS Care.* 2013;15(4):194–201.

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Supplementary Materials

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Author Disclosures

HC is a member of speaker's bureaus for Biogen, Bristol Myers Squibb, EMD Serono Research & Development Institute, Inc., Billerica, MA, USA, an affiliate of Merck KGaA, Sandoz, Sanofi Genzyme, and TG Therapeutics. She has received consulting fees from Biogen, Bristol Myers Squibb, EMD Serono Research & Development Institute, Inc., Billerica, MA, USA, an affiliate of Merck KGaA, Roche, Sanofi Genzyme, and Sandoz. She has received research grants from Atara Biotherapeutics, Anokion, Biogen, Novartis, Roche, Sanofi Genzyme, and TG Therapeutics.

RV has served on advisory boards and is a member of speaker's bureaus for Argenx, Alexion, ANI pharmaceuticals, Biogen, Bristol Myers Squibb, EMD Serono Research & Development Institute, Inc., Billerica, MA, USA, an affiliate of Merck KGaA, Genentech, Horizon Therapeutics, Janssen Pharmaceuticals, Novartis, and Sanofi Genzyme.

JK is a member of speaker's bureaus for EMD Serono Research & Development Institute, Inc., Billerica, MA, USA, an affiliate of Merck KGaA, Sanofi Genzyme, Biogen, Genentech, and Novartis.

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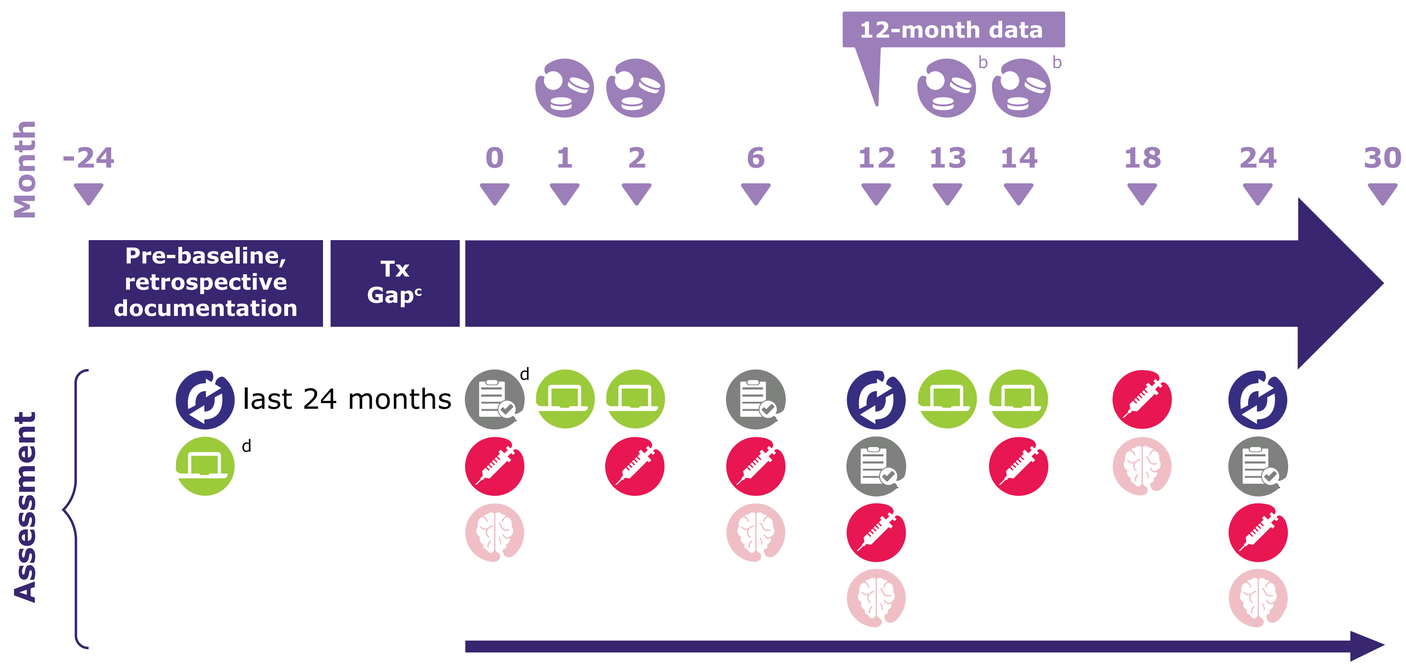
Supplementary Materials

Supplementary Figure 1. Study design[a, 1]

Key Inclusion Criteria

- Patients aged ≥18 years old
- Patients with RRMS or active SPMS treated with ≥1 course of CladT 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 CladT



[a]Please note that since the publication of the 6-month interim analysis[2], the 24-month safety extension has been removed. [b]Follow-up and assessments can be adjusted to up to 30 months depending on timing of Year 2 dose, which can be delayed up to 6 months to allow recovery of patient ALC. [c]Duration between stopping previous DMTs and starting cladribine tablets was variable and at the discretion of the treating physician. [d]First assessment is for prior DMT.

AE, adverse event; ALC, absolute lymphocyte count; BDI-FS, Beck-Depression Inventory – Fast Screen; CBC, complete blood count; DMT, disease-modifying therapy; ePRO, electronic patient-reported outcome; 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; RRMS, relapsing-remitting multiple sclerosis; SAF, safety analyses set; SF-36, 36-Item Short Form Health Survey; SPMS, Secondary-progressive multiple sclerosis; TSQM, 14-Item Treatment Satisfaction Questionnaire for Medication; Tx, treatment; WPAI-MS, Work Productivity Activity Impairment – MS.

Supplementary Table 1. MS-TAQ for CladT[a]

	CladT 3.5 mg/kg (N=187)[b]					
	Total (N=187)		Prior Oral DMTs group (n=102)		Prior Infusion DMTs group (n=85)	
	Month 1 (n=123)	Month 2 (n=127)	Month 1 (n=73)	Month 2 (n=74)	Month 1 (n=50)	Month 2 (n=53)
How many CladT were you supposed to take during this treatment week? (Mean±SD)	7.6±2.24	7.1±2.43	7.3±1.91	7.0±2.28	8.0±2.61	7.3±2.62
Did you miss or forget to take any CladT during this treatment week? n (%)						
Yes	1 (0.8)	2 (1.6)	1 (1.4)	2 (2.7)	0 (0.0)	0 (0.0)
No	121 (99.2)	125 (98.4)	71 (98.6)	72 (97.3)	50 (100)	53 (100)
Overall, how hard or easy do you feel it is to take CladT as recommended by your physician during your treatment week?[c]	n (%) 122 (99.2)	n (%) 125 (98.4)	n (%) 72 (98.6)	n (%) 73 (98.6)	n (%) 50 (100)	n (%) 52 (98.1)
	Mean±SD 1.1±0.39	Mean±SD 1.1±0.42	Mean±SD 1.1±0.32	Mean±SD 1.2±0.43	Mean±SD 1.2±0.48	Mean±SD 1.1±0.40
Overall, how satisfied are you with how things have been with your CladT treatment during your treatment week?[d]	n (%) 123 (100)	n (%) 127 (100)	n (%) 73 (100)	n (%) 74 (100)	n (%) 50 (100)	n (%) 53 (100)
	Mean±SD 4.2±0.83	Mean±SD 4.1±0.92	Mean±SD 4.2±0.75	Mean±SD 4.1±0.97	Mean±SD 4.0±0.92	Mean±SD 4.1±0.86

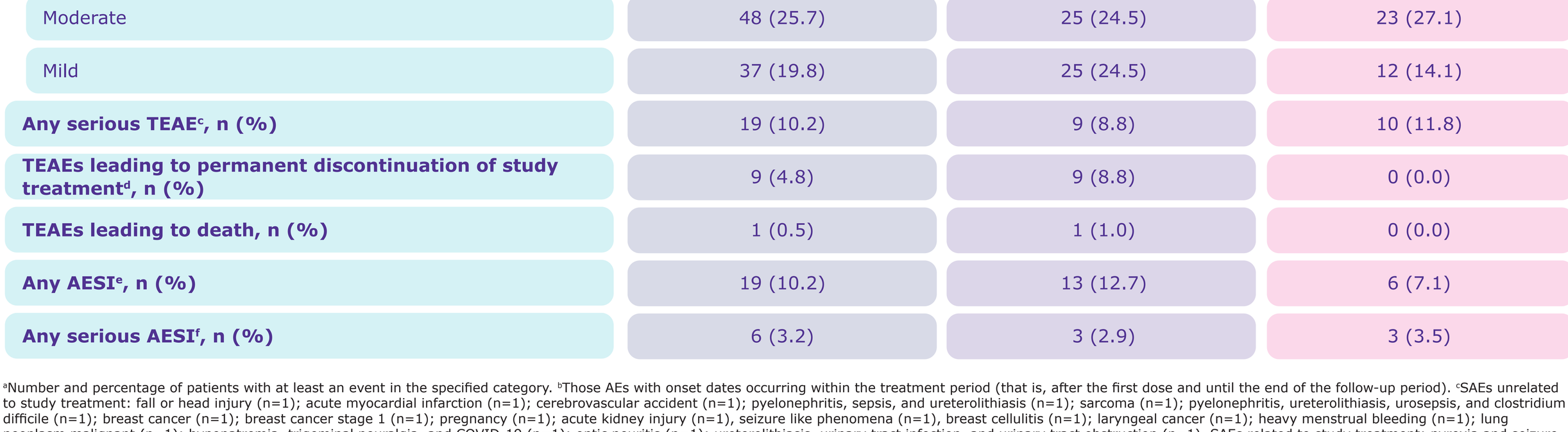
[a]Adherence to CladT is defined as the act of correctly following the treatment regimen recommended in the USPI. [b]Data in this table were based on the patient population in each month. [c]An ordinal scale from 1 to 5 was used: 1=Extremely easy, 2=A little hard, 3=Moderately hard, 4=Very hard, 5=Extremely hard. [d]An ordinal scale from 1 to 5 was used: 1=Not satisfied at all, 2=A little satisfied, 3=Moderately satisfied, 4=Very satisfied, 5=Completely satisfied.
DMT, disease-modifying therapy; MS-TAQ, MS Treatment Adherence Questionnaire; SD, standard deviation.

Supplementary Table 2. TEAEs over the 24 months of the study

	CladT 3.5 mg/kg (N=187)		
	Total[a] (N=187)	Prior Oral[a] DMTs group (n=102)	Prior Infusion[a] DMTs group (n=85)
Any TEAE[b], n (%)	102 (54.5)	59 (57.8)	43 (50.6)
Severe	17 (9.1)	9 (8.8)	8 (9.4)
Moderate	48 (25.7)	25 (24.5)	23 (27.1)
Mild	37 (19.8)	25 (24.5)	12 (14.1)
Any serious TEAE[c], n (%)	19 (10.2)	9 (8.8)	10 (11.8)
TEAEs leading to permanent discontinuation of study treatment[d], n (%)	9 (4.8)	9 (8.8)	0 (0.0)
TEAEs leading to death, n (%)	1 (0.5)	1 (1.0)	0 (0.0)
Any AESI[e], n (%)	19 (10.2)	13 (12.7)	6 (7.1)
Any serious AESI[f], n (%)	6 (3.2)	3 (2.9)	3 (3.5)

[a]Number and percentage of patients with at least an event in the specified category. [b]Those AEs with onset dates occurring within the treatment period (that is, after the first dose and until the end of the follow-up period). [c]SAEs 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 phenomena (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). SAEs related to study treatment: pyrexia and seizure (n=1); lymphocyte count decrease (n=1). One patient had multiple serious TEAEs: Not drug related: abortion threatened, drug abuse, psychogenic seizure, suicide attempt, tubo-ovarian abscess (n=1); drug-related: pyrexia and seizure like phenomena. [d]Discontinued due to lymphopenia (n=4); diarrhea, fatigue, headache, and rash (n=1); neutropenia (n=1); rash pruritic (n=1); lymphocyte count decreased; (n=1); breast cancer stage I (n=1). [e]AESI: grade 3 or 4 lymphopenia, severe infection, tuberculosis, Herpes zoster, PML, other opportunistic infections, and malignancy. [f]Distinct serious AESIs: Abortion threatened, herpes zoster, laryngeal cancer, lymphocyte count decreased, lymphopenia, neutropenia, papillary thyroid cancer, pregnancy, pyelonephritis, sarcoma, and urosepsis. AESI, adverse event of special interest; COVID-19, corona virus disease 2019; DMT, disease-modifying therapy; PML, Progressive Multifocal Leukoencephalopathy; TEAE, treatment-emergent adverse event.

Supplementary Figure 2. Lymphopenia grade[a] at Month 12 visit - SAF (N=187)[b]



[a]Lymphocyte levels reported were assessed prior to Year 2 course of CladT. [b]Patients with missing lymphocyte levels at Month 12: Total=35.8%; Switch from oral DMTs=35.3%; Switch from infusion DMTs=36.5%.
Absolute lymphocyte count levels (cells/10^3mL): Normal, 1000 to 4800; Grade 1 lymphopenia, 800 to <1000; Grade 2 lymphopenia, 500 to <800; Grade 3 lymphopenia, 200 to <500; Grade 4 lymphopenia, <200.
SAF, safety analysis set.

References:

[1]Miravalle AA, et al. *Neurodegener Dis Manag.* 2021;11(2):99–111. [2]Bass A, et al. *ACTRIMS* 2024, P493.