Clinical Outcomes of Cladribine Tablets in Aging (≥50 Years) Patients with Relapsing Multiple Sclerosis in a Real-World Setting: Insights From the 'Aging' Study

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RESEARCH IN CONTEXT

Clinical trials often exclude older patients with multiple sclerosis (MS), creating evidence gaps for treatment decisions in aging populations facing immunosenescence. This real-world study evaluates cladribine tablets (CladT) in patients aged ≥50 years, demonstrating sustained effectiveness and a favourable safety profile, and may inform age-tailored MS treatment approaches.

OBJECTIVE

To characterise the clinical outcomes after initiation of cladribine tablets (CladT) over a 24-month period in patients aged ≥50 years with relapsing forms of MS (RMS) in the US real-world setting

INTRODUCTION

Aging in patients with multiple sclerosis (MS) presents unique challenges, primarily owing to overlapping symptoms between age- and MS-related comorbidities along with immunosenescence. Immunosenescence complicates treatment decisions and patient management in older adult patients with MS.[1,2]

There is a paucity of data on the effectiveness and safety of disease-modifying therapies (DMTs) and on treatment sequencing from other DMTs to CladT for older patients in real-world settings, as MS clinical trials often exclude such patients.

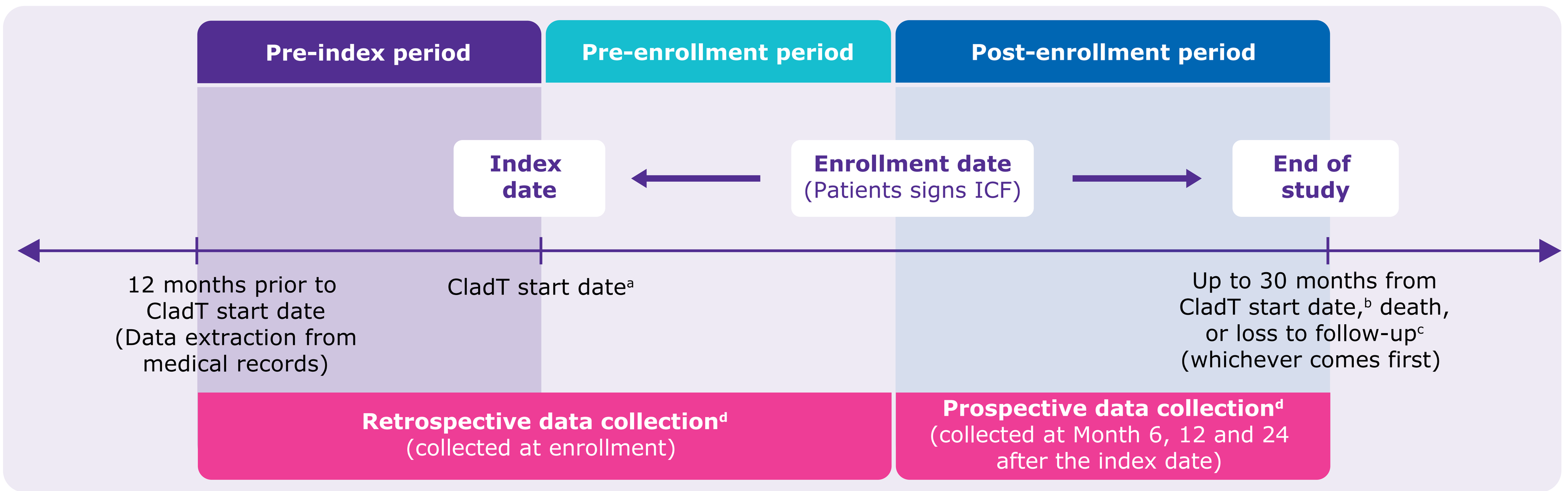
This 'Aging' study aims to report data to address that gap, adding to the currently available evidence.

METHODS

Study design

- 'Aging' is a 24-month, observational, single-arm, Phase 4, real-world study, conducted across 14 centres in the United States.
- Patients aged ≥50 years with RMS (relapsing-remitting MS [RRMS] or active secondary progressive MS [aSPMS]), who initiated treatment with CladT (3.5 mg/kg cumulative dose over 2 years per USPI[3]) on or before 31 January 2022, were included.
- The detailed study design and data collection process is shown in **Figure 1**.

Figure 1: Study design



CladT, cladribine tablets; ICF, informed consent form.
Arrows are of varying lengths for each patient as the length of the pre- and post-enrollment period depends on the index date. [a]Index date is the date of first dose of CladT. CladT start date should be on or before 31 January 2022. [b]Study protocol allows for a delay of 6 months for the start of Year 2. [c]Total study duration was approximately 36 months per patient or up to 42 months if Year 2 treatment was delayed. [d]Data were collected from medical records per the clinic's routine standard-of-care protocols. Prospective data collection was dependent on index date; for some patients, data collection may have been entirely retrospective depending on enrollment date.

Study endpoints

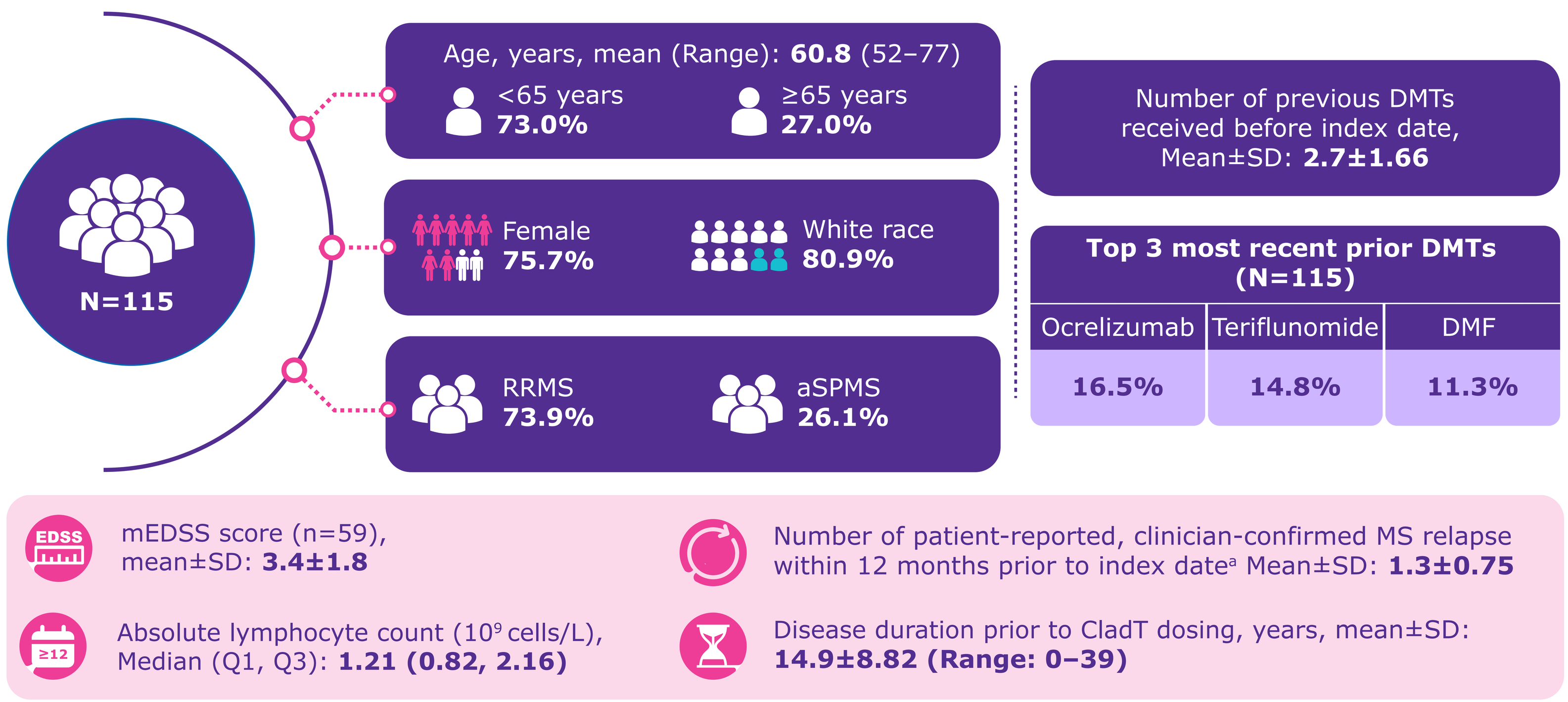
Primary endpoint	▪ **Annualised relapse rate (ARR) at 24 month** after CladT initiation[a]
Key secondary and exploratory endpoints	▪ Proportion of **patients free from MRI activity** (T1 gadolinium-enhancing [Gd+], new/enlarging T2 lesions) ▪ Number of **relapses** at **Month 6, 12**, and **24**[b] ▪ **ARR**s at **Month 6** and **12** after CladT initiation[a] ▪ **Safety** outcomes[c] ▪ **mEDSS** score

ARR, annualised relapse rate; CladT, cladribine tablets; Gd+, gadolinium-enhancing; mEDSS, modified Expanded Disability Status Scale; MRI, magnetic resonance imaging.
[a]All patients receiving ≥1 dose of CladT were analysed and ARR at Month 6, 12 and 24 after index date were reported with 95% CI using negative binomial regression models. [b]Proportion of patients free from relapse at Month 6, 12 and 24 after the index date, and the proportion of patients free from each type of MRI activity were summarised descriptively. [c]Adverse event were summarised using MedDRA classification.

RESULTS

- A total of 115 patients were included in the analysis. Key demographic and baseline (BL) characteristics are presented in **Figure 2**.

Figure 2: Demographics and baseline characteristics



aSPMS, active secondary progressive MS; BL, baseline; CladT, cladribine tablets; DMF, dimethyl fumarate; DMT, disease-modifying therapy; mEDSS, modified Expanded Disability Status Scale; MS, multiple sclerosis; RRMS, relapsing-remitting MS; SD, standard deviation.
[a]In the absence of data at the index date, the last non-missing assessment before the index date was considered as baseline.
Please refer to **Supplementary Table 1** for detailed demographics and BL characteristics, **Supplementary Table 2** for medical history, and **Supplementary Table 3** for prior DMT used for MS.

RESULTS

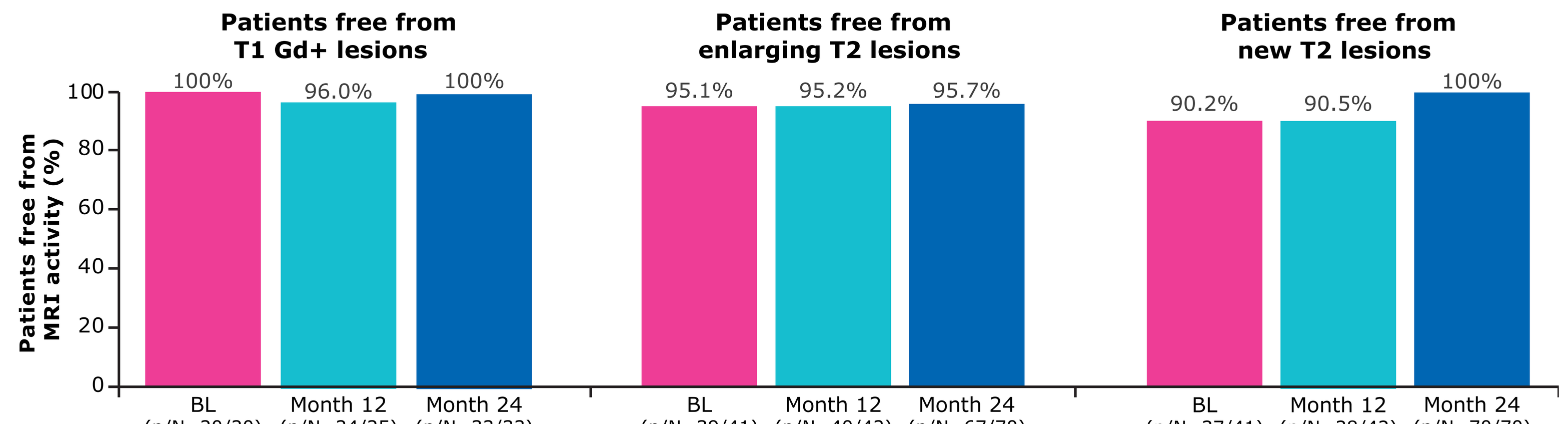
Figure 3: ARR remained low and stable over 24 months

	Month 6 (n=97)	Month 12 (n=99)	Month 24 (n=110)
Unadjusted[a] ARR over the period, Mean±SD, [95% CI[b]]	0.10±0.53 [0.00–0.21]	0.13±0.49 [0.03–0.23]	0.07±0.26 [0.03–0.12]

ARR, annualised relapse rate; CI, confidence interval; SD, standard deviation.
[a]Unadjusted ARR is calculated as the sum of the number of relapses reported over the 24-month period divided by the number of days on study between index date and last date on study and multiplied by 365.25. [b]95% CI is based on normal approximation.
Relapses refer to patient-reported, clinical-confirmed relapses reported at Month 6, 12, and 24 Visit after index date. Time period refers to period after start of CladT initiation (index date). Please refer to **Supplementary Figure 1** for results of ARR by age groups (<65 years and ≥65 years).

- **The majority of patients did not experience any relapses at any time point**; of the patients with ARR data available, the proportion of patients free from relapses were 95.9% (93/97) at Month 6; 90.9% (90/99) at Month 12 and 90.0% (99/110) at Month 24 (**Supplementary Table 4**).

Figure 4: MRI activity remained low and stable over 24 months in patients with MRI data[a]



BL, baseline; Gd+, gadolinium-enhancing, MRI, magnetic resonance imaging; MS, multiple sclerosis; n, number of patients free from corresponding type of MRI lesions; N, number of patients with available MRI activity data. [a]Data (% of patients) presented are based on number of patients with available MRI data. BL is defined as a visit occurring in the window 3 months prior to index date to 1 month post index date [-3 months, +1 month]. If there are multiple visits in the window, the visit closest to the index date will be chosen.

- Of patients with mEDSS data available, the median mEDSS scores remained stable over 24 months of treatment: 3.00 at baseline; 3.25 at Month 12, and 3.50 at Month 24 (**Supplementary Table 5**).

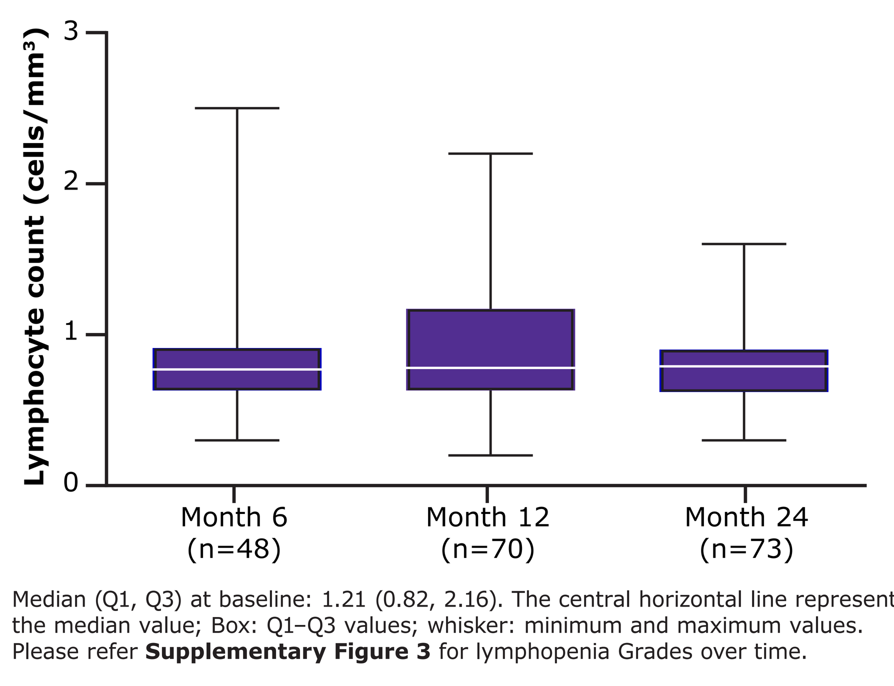
Table 1: Overall safety profile (Full analysis set; N=115)

Parameters	n (%)
Patients with any AE[a]	**80 (69.6)**
Most common AEs	
Lymphopenia	51 (44.3)
COVID-19	15 (13.0)
UTI	7 (6.1)
Patients with any severe AE	**14 (12.2)**
Most common severe AE: Infections[b]	2 (1.7)
Patients with any SAE[c]	**8 (7.0)**
AEs leading to treatment discontinuation[d]	**9 (7.8)**
Most common reason: Lymphopenia	6 (5.2)
Death	**0**
Malignancy	**0**

AE, adverse events; COVID, corona virus disease; SAE, serious AE; UTI, urinary tract infection.
[a]An AE is defined as any untoward medical occurrence in a patient or clinical study patient administered a pharmaceutical product and which does not necessarily have a causal relationship with cladribine tablets. [b]Severe infections: UTI, 1 (0.9); pneumonia, 1 (0.9). [c]Serious AEs: small intestinal obstruction, 2 (1.7); pneumonia, 1 (0.9); UTI, 1 (0.9); multiple sclerosis pseudo relapse, 1 (0.9); optic neuritis, 1 (0.9); paraesthesia, 1 (0.9); asthenia, 1 (0.9); femur fracture, 1 (0.9); mental status changes, 1 (0.9). [d]Reasons for treatment discontinuation: Lymphopenia: 6 (5.2); herpes ophthalmic: 1 (0.9); burning sensation: 1 (0.9); rashes: 1 (0.9).
Please refer **Supplementary Table 6** for adverse drug reaction and pre-specified potential safety event and **Supplementary Table 7** for severe AEs.

- Overall safety profile was favourable and consistent with that reported in other clinical trials.
- Herpes infection was reported in two cases (1.8%), one herpes ophthalmic and one herpes zoster, both of moderate severity.

Figure 5: Median lymphocyte counts (0.8) were stable over time



- At Month 24, among patients with lymphocyte data, the majority of AEs reported for lymphopenia were mild-to-moderate in severity (Grade 1: 20.0%; Grade 2: 27.0%), Grade 3 reported in 6.1% of patients and no Grade 4 lymphopenia reported (**Supplementary Figure 2**).

Median (Q1, Q3) at baseline: 1.21 (0.82, 2.16). The central horizontal line represents the median value; Box: Q1–Q3 values; whisker: minimum and maximum values.
Please refer **Supplementary Figure 3** for lymphopenia Grades over time.

CONCLUSIONS

- **In older patients with MS, ARR over 24 months after CladT treatment was low at 0.07 with the majority of patients not experiencing relapses.**
- **At Month 24, among patients with MRI data, >95% were free of new or enlarging T2 lesions, and 100% were free from T1 Gd+ lesions.**
- **CladT showed a favourable safety profile in an older population with no new or unexpected safety concerns identified; the rate of SAEs was consistent with that reported in other CladT clinical trials.**
- **At Month 24, among those with lymphocyte data, most reported instances of lymphopenia were Grade 1 or 2 (47%), with 6.1% of patients experiencing Grade 3 lymphopenia. No Grade 4 lymphopenia was reported.**
- **These results support the favourable benefit–risk profile of CladT in aging patients with MS (aged ≥50 years) and may help inform decision making in the treatment of this population.**

SCAN FOR AFFILIATIONS, DISCLOSURES AND SUPPLEMENTARY MATERIALS

References: 1. de Seze J, et al. Neurol Ther. 2024 Jun;13(3):519-533; 2. Arun T, et al. ACNR, Advances in Clinical Neuroscience and Rehabilitation. 2025 Apr 6; 3. MAVENCLAD US Prescribing Information, May 2024.

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Supplementary Materials

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Author Disclosures

JK served in the scientific advisory board for Genentech, EMD Serono Research & Development Institute, Inc., Billerica, MA, USA, an affiliate of Merck KGaA, and Novartis, and received speaker fees from Biogen, Genentech, EMD Serono Research & Development Institute, Inc., Billerica, MA, USA, an affiliate of Merck KGaA, Novartis, and TG Therapeutics.

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Supplementary Materials

Supplementary Table 1: Demographics and baseline characteristics

Parameters	N=115
Age, years (mean±SD)	60.8±5.99
Gender, n (%)	
Female	87 (75.7)
Male	28 (24.3)
Race, n (%)	
White	93 (80.9)
Black or African American	6 (5.2)
Other/Unknown[a]	16 (13.9)
Ethnicity, n (%)	
Hispanic	14 (12.2)
Non-Hispanic	70 (60.9)
Unknown	31 (27.0)

BL, baseline; SD, standard deviation.

Percentages are calculated based on the full analysis set. BL refers to treatment continuation baseline. Data cut-off: 22 January 2025. [a]More than one race: Black or African American, American Indian or Alaska Native.

Supplementary Table 2: Medical history (N=115)

Parameters	n (%)
Patients with any relevant medical history event or comorbidity	111 (96.5)
Medical history (PT) in >10% of patients	
Depression	41 (35.7)
Hypertension	41 (35.7)
Anxiety	26 (22.6)
Fatigue	26 (22.6)
Vitamin D deficiency	26 (22.6)
Hyperlipidaemia	25 (21.7)
Gastroesophageal reflux disease	19 (16.5)
Migraine	19 (16.5)
Asthma	18 (15.7)
Hypothyroidism	17 (14.8)
Insomnia	17 (14.8)
Lymphopenia	14 (12.2)
Muscle spasms	14 (12.2)
Vitamin B12 deficiency	13 (11.3)
Muscle spasticity	12 (10.4)

DMT, disease modifying therapy; MS, multiple sclerosis; PT, preferred term.
Data cut-off: 22 January 2025. Percentages are calculated based on the full analysis set.

Supplementary Table 3: Most recent prior DMTs used for MS (N=115)

Parameters	n (%)
Any DMT prescribed for MS	**110 (95.7)**
Most recent prior DMTs	
Ocrelizumab	19 (16.5)
Teriflunomide	17 (14.8)
Interferons	15 (13.1)
Dimethyl fumarate	13 (11.3)
Fingolimod/Fingolimod hydrochloride	13 (11.3)
Natalizumab	12 (10.4)
Glatiramer acetate/Glatiramer	8 (7.0)
Alemtuzumab	4 (3.5)
Siponimod	4 (3.5)
Rituximab[a]	2 (1.7)
Diroximel fumarate	1 (0.9)
Ofatumumab	1 (0.9)
Ozanimod	1 (0.9)

CRF, case report form; DMT, disease modifying therapy; MS, multiple sclerosis.

Data cut-off: 22 January 2025. Percentages are calculated based on the full analysis set. A patient can have one or more prior DMTs reported. Most recent previous DMT is defined as the last or latest DMT that a patient reported on the prior DMT CRF. [a]Rituximab is used off-label as a DMT for MS.

Supplementary Figure 1: ARR[a] over the 24 months by age group

	Month 6		Month 12		Month 24	
	Age <65y (n=70)	Age ≥65y (n=27)	Age <65y (n=72)	Age ≥65y (n=27)	Age <65y (n=80)	Age ≥65y (n=30)
Unadjusted ARR[a] over the period, Mean±SD, [95% CI[b]]	0.14±0.62 [0.01–0.29]	0	0.18±0.57 [0.05–0.31]	0	0.10±0.30 [0.03–0.16]	0.02±0.09 [0.02–0.05]
Number of patients with relapses, n (%)						
0	66 (78.6)	27 (87.1)	63 (75.0)	27 (87.1)	70 (83.3)	29 (93.5)
1	3 (3.6)	0	7 (8.3)	0	7 (8.3)	1 (3.2)
≥2	1 (1.2)	0	2 (2.4)	0	3 (3.6)	0

ARR, annualised relapse rate; CI, confidence interval; SD, standard deviation; y, years.

[a]Unadjusted ARR is calculated as the sum of the number of relapses reported over the 24-month period divided by the number of days on study between index date and last date on study and multiplied by 365.25. [b]95% CI is based on normal approximation.

Relapses refer to patient-reported, clinical-confirmed relapses reported at Month 6, 12, and 24 Visit after index date. Time period refers to period after start of CladT initiation (index date).

Supplementary Table 4: Number of relapses over the 24 months

	Month 6	Month 12	Month 24
Number of patients with relapses, n (%)			
0	93 (80.9)	90 (78.3)	99 (86.1)
1	3 (2.6)	7 (6.1)	8 (7.0)
≥2	1 (0.9)	2 (1.7)	3 (2.6)

Supplementary Table 5: mEDSS Scores Over Time (N=115)

	Baseline	Month 6	Month 12	Month 24
mEDSS score				
n (%)	59 (51.3)	56 (48.7)	64 (55.7)	76 (66.1)
Missing, n (%)	56 (48.7)	59 (51.3)	51 (44.3)	39 (33.9)
Median (Q1, Q3)	3.00 (2.00, 4.50)	3.00 (2.00, 5.00)	3.25 (2.00, 5.00)	3.50 (2.00, 4.50)

mEDSS, modified Expanded Disability Status Scale.

Supplementary Table 6: Safety profile – ADRs and PPSE (N=115)

Parameters	n (%)[b]
Patients with any ADR[a]	56 (48.7)
Most common ADR: Lymphopenia	48 (41.7)
Patients with any SADRs	1 (0.9)
UTI	1 (0.9)
ADRs leading to treatment discontinuation[c]	9 (7.8)
Lymphopenia	6 (5.2)
Death	0
Patients with any PPSE[d]	39 (33.9)
Lymphopenia	36 (31.3)
Patients with any serious PPSE	2 (1.7)
Pneumonia	1 (0.9)
UTI	1 (0.9)

ADR, adverse drug reaction; n, number of patients experiencing the event; N, number of patients in the safety analysis set; PPSE, pre-specified potential safety event; SADRs, serious ADRs; UTI, urinary tract infection.

[a]An ADR is defined as a response to a medicinal product which is noxious and unintended. [b]Percentages were calculated based on the safety analysis set; Patients were counted once per system organ class and once per preferred term. [c]Other reasons for treatment discontinuation: Herpes ophthalmic: 1 (0.9); burning sensation: 1 (0.9); rashes: 1 (0.9). [d]PPSE is defined based on a search list of MedDRA codes including malignancies, severe infections, opportunistic infections, progressive multifocal leukoencephalopathy, and severe lymphopenia.

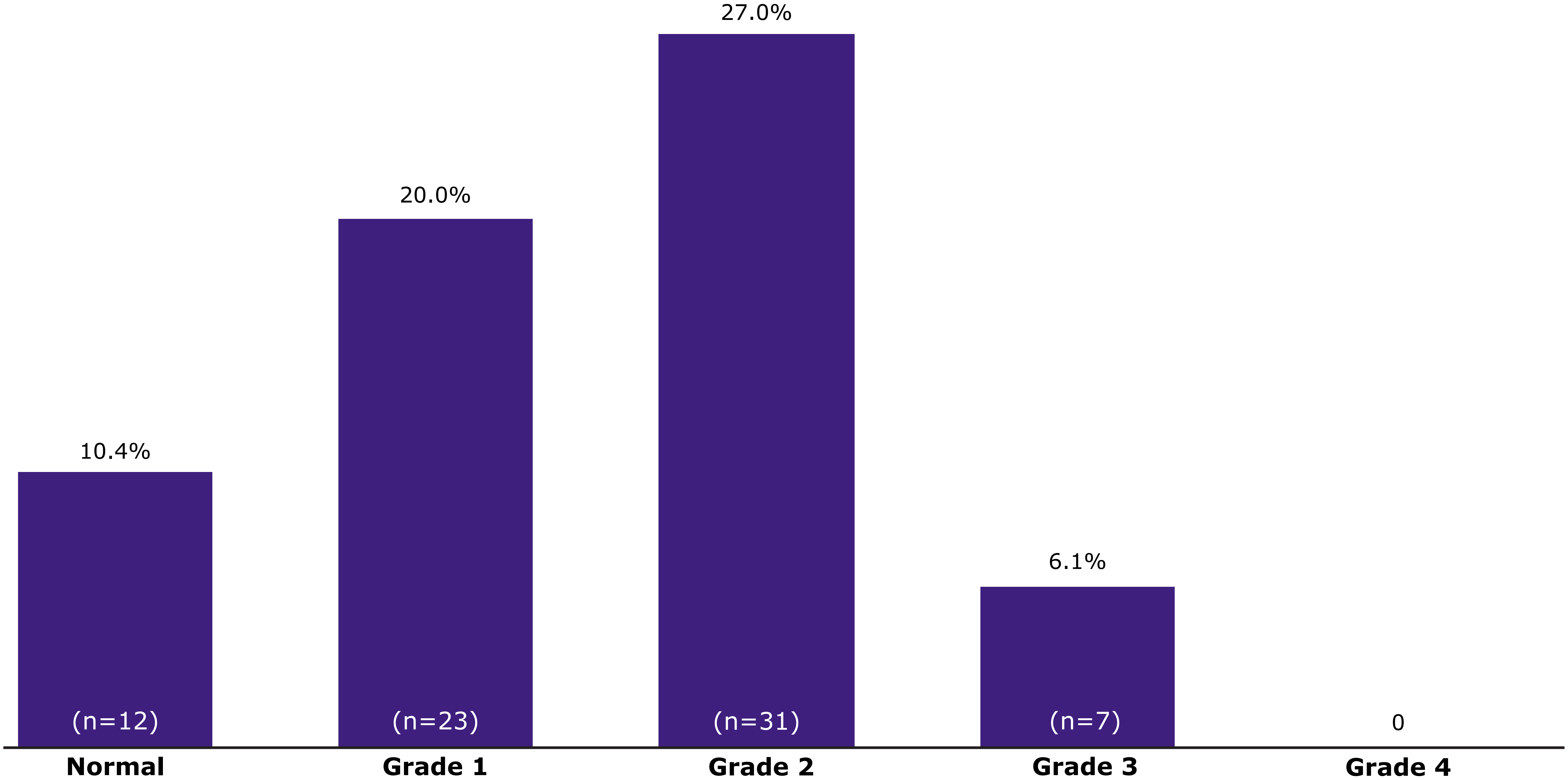
Supplementary Table 7: Safety profile - Severe AEs

Parameters	n (%)
Patients with any severe AE	14 (12.2)
Lymphopenia	4 (3.5)
Small intestinal obstruction	2 (1.7)
UTI	1 (0.9)
Pneumonia	1 (0.9)
Intervertebral disc degeneration	1 (0.9)
Pain in jaw	1 (0.9)
Scoliosis	1 (0.9)
Asthenia	1 (0.9)
Stenosis	1 (0.9)
Femur fracture	1 (0.9)
Mental status changes	1 (0.9)
Craniotomy	1 (0.9)

AE, adverse events; UTI, urinary tract infection.

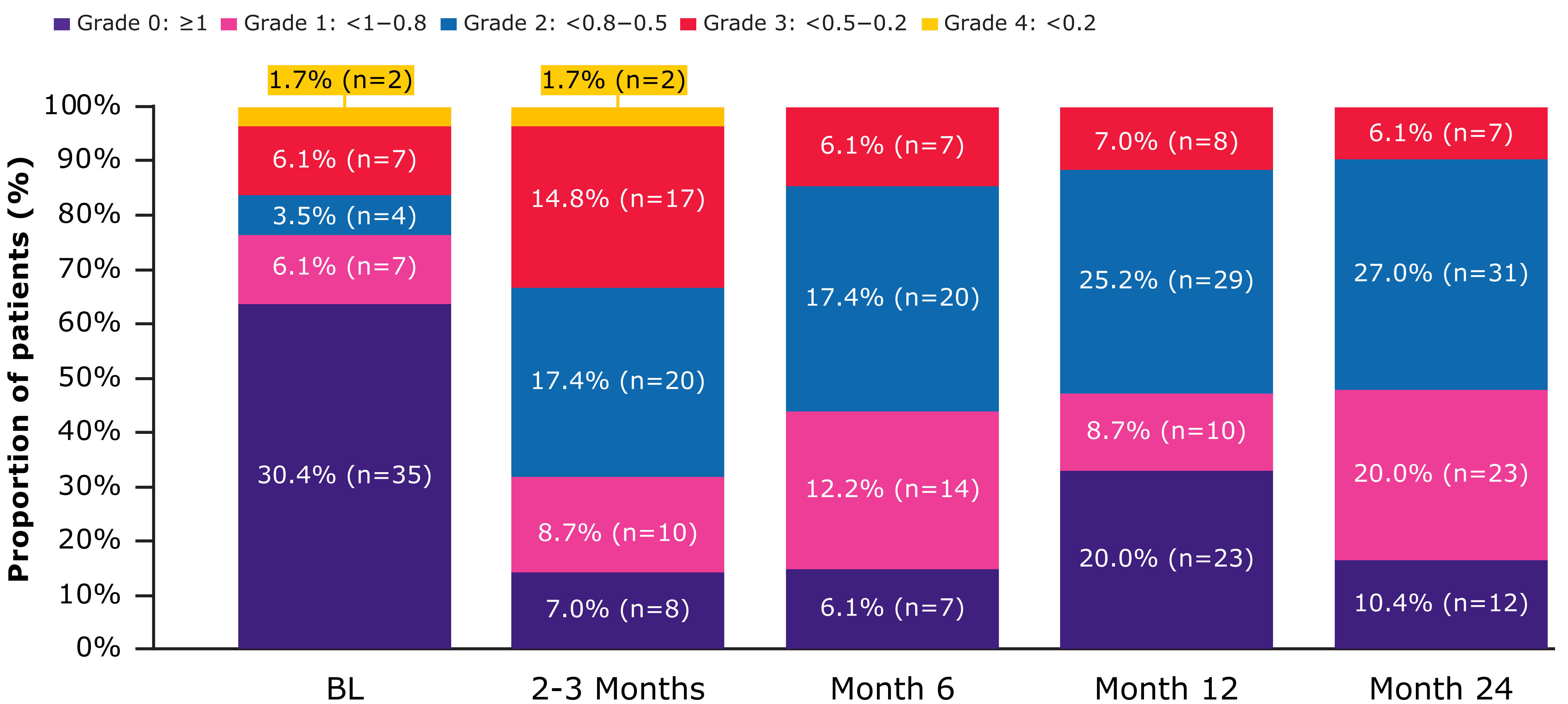
Supplementary Materials

Supplementary Figure 2: Lymphopenia at Month 24 (N=115)



Lymphopenia Grade: Normal: ≥1; Grade 1: <1−0.8; Grade 2: <0.8−0.5; Grade 3: <0.5−0.2; Grade 4: <0.2. Data for lymphopenia grades at Month 24 were missing for 36.5% (N=42) of patients.

Supplementary Figure 3: Lymphopenia Grades over time (N=115)



BL, Baseline.
Data for lymphopenia grades were missing for the following patients: at BL, 52.2% (n=60); at 2-3 months, 50.4% (n=58); at Month 6, 58.3% (n=67); at Month 12, 39.1% (n=45); and at Month 24, 36.5% (n=42).