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Treatment satisfaction, safety, and tolerability of cladribine tablets in patients with highly active relapsing multiple sclerosis: CLARIFY-MS study 6-month interim analysis

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ABSTRACT

Background Multiple sclerosis (MS) is a chronic disabling disease that is associated with negative effects on health-related quality of life (HRQoL) due to reduced physical and psychosocial functioning. Cladribine tablets 10 mg (3.5 mg/kg cumulative dose over 2 years) have been approved for the treatment of adult patients with highly active relapsing multiple sclerosis (RMS). The ongoing CLARIFY-MS study (NCT03369665; EudraCT number: 2017-002632-17) aims to assess the effect of cladribine tablets 3.5 mg/kg on HRQoL of patients with highly active RMS.

Objective To report on the design of the CLARIFY-MS study, baseline patient characteristics, and results of a pre-planned interim analysis focusing on treatment satisfaction, safety, and tolerability that includes all data reported till 6 months after start of treatment.

Methods The CLARIFY-MS study is a 2-year, open-label, single-arm, prospective, multicenter, phase IV study. Eligible patients with highly active RMS were assigned to receive cladribine tablets 3.5 mg/kg over 2 years. Treatment satisfaction was assessed using the Treatment Satisfaction Questionnaire for Medication (TSQM, v1.4; scale range from 0 to 100, higher values indicating higher satisfaction). Safety assessments, including occurrence of treatment-emergent adverse events (TEAEs; any adverse event reported after drug administration), serious adverse events (SAEs), and lymphocyte counts, were summarized descriptively.

Results A total of 482 patients from 85 sites in Europe were treated with cladribine tablets. Mean patient age was 37.4 years, 338 (70.1%) were women, median EDSS was 2.5, and 345 (71.6%) were prior users of disease-modifying therapy (DMT). During the first 6 months after the start of treatment, and before reaching the full dose of cladribine tablets, mean TSQM global satisfaction score for the overall population was 70.4 (standard deviation, ± 18.48). The side effects score was 91.9 (± 17.68), convenience scored 86.6 (± 13.57), and effectiveness

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was 65.8 (± 21.14). A total of 275 patients (57.1%) reported at least one TEAE and 9 patients (1.9%) had a SAE. The majority of observed lymphopenia cases were of grade 1 or 2; 33 (6.8%) of the total study cohort had grade 3 lymphopenia, and no grade 4 lymphopenia was reported.

Conclusion Patients reported high treatment satisfaction (TSQM) with cladribine tablets in this pre-planned interim analysis at 6 months. Few serious, and no unexpected, adverse events were reported, and there were no instances of grade 4 lymphopenia over the first 6 months. These preliminary data indicate good tolerability and convenience of administration of cladribine tablets in patients with highly active RMS.

1. Introduction

Multiple sclerosis (MS) is a chronic disabling disease that is associated with negative effects on health-related quality of life (HRQoL) due to reduced physical and psychosocial functioning (Jongen, 2017; Oreja-Guevara, 2015; Orme et al., 2007; Pashazadeh Kan et al., 2020; Epub ahead of print). Cladribine tablets 10 mg (3.5 mg/kg cumulative dose over 2 years) have been approved for the treatment of adult patients with highly active relapsing multiple sclerosis (RMS). Treatment is administered as two annual courses, each of 2 weeks and administered 1 month apart; no additional treatment is required in years 3 and 4 (EMD Serono, 2019; Merck Europe B.V., 2021).

In the CLARITY study, treatment with cladribine tablets was associated with a decreased need for medical and societal support and improved HRQoL (Afolabi et al., 2018; Ali et al., 2012). However, effects on HRQoL, cognition, employment status, and treatment satisfaction need to be further explored. Indeed, higher treatment satisfaction is generally associated with fewer relapses and lower disability scores (Haase et al., 2016). As such, it is important to investigate patient-reported responses to assess treatment satisfaction and supplement clinical trial data.

The ongoing CLARIFY-MS study (NCT03369665; EudraCT number: 2017–002632–17) aims to assess the effect of cladribine tablets 3.5 mg/kg on HRQoL in patients with highly active RMS. In this paper, we report on the design of the CLARIFY-MS study and baseline patient characteristics, and summarize the results of a pre-planned interim analysis focusing on treatment satisfaction, safety, and tolerability that includes all data reported till 6 months after start of treatment.

2. Methods

2.1. Study design and patients

The CLARIFY-MS study is a 2-year, open-label, single-arm, prospective, multicenter, phase IV study. Eligible patients with highly active RMS receive open-label cladribine tablets 3.5 mg/kg body weight over 2 years, administered as one treatment course of 1.75 mg/kg body weight per year with each treatment course consisting of 2 weeks of active treatment (week 1 and week 5 of each year). The study visits and assessments at each visit are captured in **Fig. 1**.

The primary objective of CLARIFY-MS is to assess HRQoL through the MS QoL 54-item questionnaire (MSQoL-54) in highly active RMS patients treated with cladribine tablets for 2 years. To assess this objective, the primary endpoint is the change in MSQoL-54 (physical and mental health composite scores) at 24 months compared to baseline. The secondary objective is to examine treatment satisfaction of cladribine tablets, assessed through the Treatment Satisfaction Questionnaire for Medication (TSQM, v1.4) at 6 months of treatment. This endpoint was the main focus of a pre-planned interim analysis (reported here), conducted when all patients had completed the 6-month assessment. The TSQM is a simple, non-MS specific, and widely used treatment satisfaction questionnaire in studies of patients with MS (Atkinson et al., 2004), which has good psychometric properties (Vermersch et al., 2017). Global satisfaction is assessed based on confidence in benefits, a balance between good and bad effects, and overall satisfaction with a score from 0 to 100 (higher numbers indicate higher satisfaction) (**Supplementary Figure 1**). Tertiary objectives of CLARIFY-MS include: assessment of: safety and tolerability of cladribine tablets; the effect of treatment on the progression of disability, cognition, and brain atrophy; and to establish correlations between clinical outcomes and HRQoL with treatment satisfaction. The full list of tertiary endpoints is provided in the **supplementary material**.

In order for patients to be included in CLARIFY-MS they were required to meet all of the following criteria: adults aged ≥18 years with highly active RMS (defined as one relapse in the previous year and a total lesion count of ≥1 T1 Gd+ lesion or ≥9 T2 lesions while on therapy with another disease-modifying therapy [DMT] or ≥2 relapses in the previous year regardless of prior DMT) and an Expanded Disability

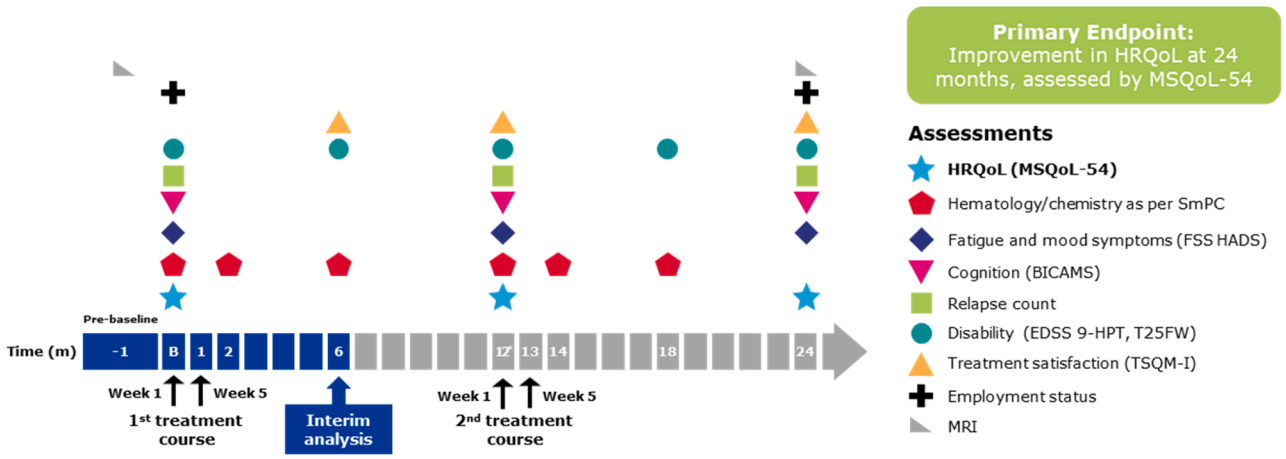


Fig. 1. CLARIFY-MS study design
9-HPT, 9-hole peg test; B, baseline; BICAMS, Brief International Cognitive Assessment for Multiple Sclerosis; EDSS, Expanded Disability Status Scale; FSS, Fatigue Severity Scale; HADS, Hospital Anxiety and Depression Scale; HRQoL, health-related quality of life; MRI, magnetic resonance imaging; MSQoL-54, Multiple Sclerosis Quality of Life-54; SmPC, Summary of Product Characteristics; T25FW, timed 25-foot walking test; TSQM, Treatment Satisfaction Questionnaire for Medication.

Status Scale (EDSS) score of ≤5.0. The following three criteria were to be met for establishing a relapse: 1) Neurological abnormality, either newly appearing or re-appearing. The abnormality must be separated by at least 30 days from onset of a preceding clinical event, and last for at least 24 h. 2) Absence of fever (>37.5 °C / 99.5°F) or known infection. 3) Objective neurological impairment, correlating with the subject's reported symptoms, defined as either an increase in at least one of the functional system scores of the EDSS, or an increase of the total EDSS score. Females were required to not be pregnant or breast-feeding, and all patients were required to use contraception. Screening MRIs were performed for all patients. For patients switching to cladribine tablets from any DMT historically linked to progressive multifocal leukoencephalopathy (PML) as an adverse event, the absence of PML on their screening MRI was required (and confirmed by independent central viewers).

Patients were excluded if they had one or more of the following: any signs of PML or major central nervous system disease other than MS; positive test for human immunodeficiency virus (HIV), hepatitis C, hepatitis B, and tuberculosis; and immunocompromised clinical status (including patients receiving immunosuppressive or myelosuppressive therapy). The full inclusion and exclusion criteria are listed in the **supplementary material**.

The study was performed according to principles in the Declaration of Helsinki and International Council for Harmonisation Guidelines for Good Clinical Practice (ICH GCP). Written informed consent was required from study participants before any trial-related activities were carried out. A patient information sheet was prepared in accordance with ICH GCP for the purpose of obtaining informed consent.

2.2. Interim analysis

A pre-planned interim analysis was conducted after all patients had completed the 6-month assessment, before reaching a full dose of cladribine tablets. The interim analysis is considered to be supportive of the final 2-year analysis. Due to the exploratory nature of the study, no alpha spending functions were planned to control for overall type I error inflation. The cut-off date was defined for each patient individually, either at the Month 6 visit date, or 180 days after the start of cladribine tablets if the visit date was missing. The full analysis set for efficacy consisted of all patients who were classified as eligible and treated with at least one dose of cladribine tablets. The safety analysis set consisted of all patients who were treated with at least one dose of cladribine tablets. Subgroup analysis split patients into treatment naïve and prior DMT users (previous treatment with DMTs any time before initiating cladribine tablets).

Results for the TSQM global satisfaction score are presented. The analysis used a mixed-effects linear model to estimate the TSQM global satisfaction score at 6 months, after adjusting for age, EDSS at baseline, and within-country correlation (Scandinavian countries were pooled). Treatment effectiveness, side effects, and convenience, as assessed by TSQM, are also summarized using descriptive statistics. Occurrence of relapses, adverse events, and lymphocyte counts are summarized descriptively. Lymphocyte counts were categorized using NCI-CTCAE version 5.0 (grade 2, <0.8–0.5 × 10^9/L; grade 3, <0.5–0.2 × 10^9/L; grade 4, <0.2 × 10^9/L), and summarized by worst grade per patient.

3. Results

This ongoing study has enrolled 554 patients, who provided informed consent, at a total of 85 sites in 18 European countries between June 2018 and April 2019. There were 485 eligible patients; three patients did not receive treatment, and therefore the full analysis set for this interim analysis comprised 482 patients (CONSORT diagram shown in **Supplementary Figure 2**).

3.1. Baseline characteristics and prior disease-modifying therapy

Patients had a mean age of 37.4 years and most were female (70.1%); a total of 345 patients (71.6%) were prior DMT users (Table 1). Among patients who had received DMT in the 6 months before cladribine treatment, patients mainly switched from interferons (28.9%) and dimethyl fumarate (22.2%). Other common preceding treatments included glatiramer acetate (14.4%), teriflunomide (13.7%), and fingolimod (13.4%) (Table 1).

Baseline demographics were generally comparable among patients who were treatment naïve and the subgroup who had received prior DMT; as expected, patients with prior DMT use tended to have a longer disease duration than those who were treatment naïve. Mean time since onset of MS was 46.1 months versus 120.1 months, and mean time since first relapse was 21.3 months versus 85.5 months, in the treatment naïve and prior DMT subgroups, respectively.

3.2. Treatment satisfaction

The mean global satisfaction score was 70.4 (standard deviation, ± 18.5) for the total study cohort, 69.5 (± 18.7) for treatment naïve patients, and 70.8 (± 18.4) for those with prior DMT use. After adjustment for age and EDSS at Baseline, the mean global satisfaction score was 70.0

Table 1
Baseline characteristics and prior disease-modifying therapy of patients in CLARIFY-MS (full analysis set).

	Treatment naïve $n = 137$	Prior DMT $n = 345$	Total study cohort $n = 482$
Age, mean ± SD, years	35.4 ± 11.46	38.2 ± 9.83	37.4 ± 10.39
Female, n (%)	91 (66.4)	247 (71.6)	338 (70.1)
Time since onset of MS, mean ± SD, months	46.1 ± 70.5	120.1 ± 88.0	99.1 ± 89.8
Time since the first clinical episode, mean ± SD, months	21.3 ± 41.1	85.5 ± 81.6	67.5 ± 78.1
Relapses in prior 12 months, n (%)			
0	0	7 (2.0)	7 (1.5)
1	40 (29.2)	233	273 (56.6)
2	87 (63.5)	(67.5)	181 (37.6)
>2	10 (7.3)	94 (27.2)	21 (4.4)
		11 (3.2)	
EDSS, median (range)	2.0 (0–5.0)	2.5 (0–5.0)	2.5 (0–5.0)
DMT use in prior 6 months,[a] n (%)		284 (82.3)	
Last DMT within 6 months of start of study medication, n (%)[b]			
Interferons		82 (28.9)	
Interferon beta-1a		53 (18.7)	
Interferon beta-1b		15 (5.3)	
Peginterferon beta-1a		11 (3.9)	
Interferon		1 (0.4)	
Interferon beta		1 (0.4)	
Peginterferon		1 (0.4)	
Dimethyl fumarate		63 (22.2)	
Glatiramer acetate		41 (14.4)	
Teriflunomide		39 (13.7)	
Fingolimod		38 (13.4)	
Natalizumab		7 (2.5)	
Investigational drug		5 (1.8)	
Daclizumab		4 (1.4)	
Diroximel fumarate		3 (1.1)	
Methotrexate		1 (0.4)	
Ozanimod		1 (0.4)	

[a] At least one DMT within 6 months prior to cladribine tablets treatment.
[b] Percentages are of the total patients ($n = 284$) who received at least one DMT within 6 months prior to cladribine tablets treatment.

DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; SD, standard deviation.

(95% confidence interval, 66.7–73.5) for the total study cohort, 68.7 (62.1–75.4) for treatment naïve patients, and 70.2 (66.4–74.0) for prior DMT users (Fig. 2). Scores for treatment effectiveness, side effects, and convenience were similar between the treatment naïve and prior DMT subgroups (Table 2). The median side effects score was the maximum 100 for both subgroups and the total population.

3.3. Occurrence of relapses

The overall number of patients with at least one relapse at 6 months was 42 (8.7%; including 12 [8.8%] treatment naïve patients and 30 [8.7%] prior DMT users).

3.4. Safety and tolerability

A total of 275 patients (57.1%) reported at least one treatment-emergent adverse event (TEAE, any adverse event reported after drug administration) (Table 3). The proportion of patients with a mild or moderate treatment-related TEAE was 18.7% and 9.1%, respectively; few patients (0.6%, $n = 3$) experienced severe treatment-related TEAEs. There were seven cases (1.5%) of herpes zoster recorded in total, including two (1.5%) treatment naïve patients and five (1.4%) prior DMT users. Three patients (0.6%) had a TEAE that led to a temporary discontinuation of treatment, and one patient (0.2%) had a TEAE that led to permanent treatment discontinuation (advanced ovarian carcinoma [as per biopsy], 5 months after starting treatment with cladribine tablets).

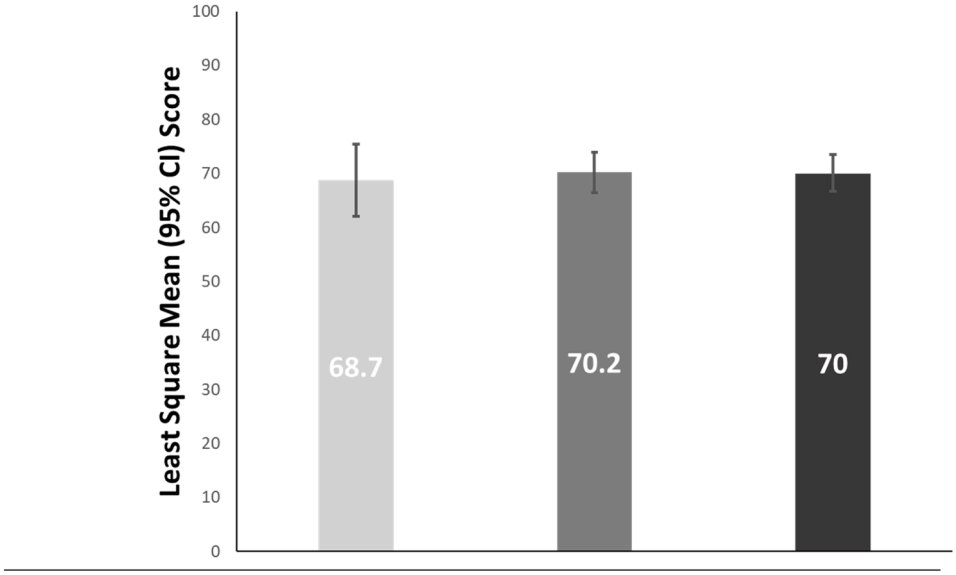
Nine patients (1.9%) had a serious adverse event (SAE). Of these SAEs, four were considered related to study treatment all of which were overdoses. No change in medication dosage was required. The remaining SAEs deemed unrelated to study treatment included a medication error, panic disorder, ovarian cyst, and aortic aneurysm. There were no deaths reported in the study.

The majority of potentially drug-induced lymphopenia cases were of grade 1 or 2; 33 patients (6.8%) of the total study cohort had grade 3 lymphopenia, and no grade 4 lymphopenia was reported. Lymphopenia was more commonly reported in prior DMT users compared with the

Table 2
TSQM scores at 6 months (full analysis set).

TSQM scores	Treatment naïve n = 137	Prior DMT n = 345	Total study cohort n = 482
Global satisfaction			
Mean ± SD	69.5 ± 18.71	70.8 ± 18.40	70.4 ± 18.48
Median	71.4	71.4	71.4
Side effects			
Mean ± SD	92.7 ± 17.85	91.5 ± 17.63	91.9 ± 17.68
Median	100	100	100
Convenience			
Mean ± SD	88.0 ± 13.71	86.1 ± 13.51	86.6 ± 13.57
Median	94.4	88.9	88.9
Effectiveness			
Mean ± SD	65.1 ± 20.99	66.1 ± 21.23	65.8 ± 21.14
Median	66.7	66.7	66.7

DMT, disease-modifying therapy; SD, standard deviation; TSQM, Treatment Satisfaction Questionnaire for Medication.



	Treatment naïve n = 137	Prior DMT n = 345	Total study cohort n = 482
Estimated least square mean (95% CI)	68.7 (62.06–75.39)	70.2 (66.36–73.97)	70.0 (66.69–73.46)

CI, confidence interval; DMT, disease-modifying therapy; TSQM, Treatment Satisfaction Questionnaire for Medication

Fig. 2. Global satisfaction score at 6 months (using TSQM v1.4)
CI, confidence interval; DMT, disease-modifying therapy; TSQM, Treatment Satisfaction Questionnaire for Medication.

Table 3
Summary of treatment-emergent adverse events (safety analysis set).

Number of patients with:	Treatment naïve $n = 137$	Prior DMT $n = 345$	Total study cohort $n = 482$
Any TEAE, n (%)	82 (59.9)	193 (55.9)	275 (57.1)
≥1 study-treatment related TEAE, n (%)	38 (27.7)	99 (28.7)	137 (28.4)
Any TEAE by severity,[a] n (%)			
Mild	27 (19.7)	63 (18.7)	90 (18.7)
Moderate	9 (6.6)	44 (18.3)	44 (9.1)
Severe	2 (1.5)	35 (10.1)	3 (0.6)
		2 (0.3)	
Any serious TEAE, n (%)	3 (2.2)	6 (1.7)	9 (1.9)
Any TEAE leading to death, n (%)	0	0	0
Any TEAE leading to temporary discontinuation of study treatment, n (%)	0	3 (0.9)	3 (0.6)
Any TEAE leading to permanent discontinuation of study treatment, n (%)	0	1 (0.3)	1 (0.2)
TEAEs observed in ≥2% of total patients, n (%)			
Headache	21 (15.3)	42 (12.2)	63 (13.1)
Lymphopenia	5 (3.6)	35 (10.1)	40 (8.3)
Nasopharyngitis	14 (10.2)	16 (4.6)	30 (6.2)
Upper respiratory tract infection	9 (6.6)	11 (3.2)	20 (4.1)
Back pain	6 (4.4)	11 (3.2)	17 (3.5)
Urinary tract infection	1 (0.7)	15 (4.3)	16 (3.3)
Nausea	4 (2.9)	11 (3.2)	15 (3.1)
Fatigue	9 (6.6)	5 (1.4)	14 (2.9)
Alopecia	3 (2.2)	10 (2.9)	13 (2.7)
Influenza	5 (3.6)	7 (2.0)	12 (2.5)
Bronchitis	2 (1.5)	9 (2.6)	11 (2.3)
Oral herpes	4 (2.9)	7 (2.0)	11 (2.3)
Lymphocyte count decreased	1 (0.7)	9 (2.6)	10 (2.1)
Pain in extremity	4 (2.9)	6 (1.7)	10 (2.1)

DMT, disease-modifying therapy; TSQM, Treatment Satisfaction Questionnaire for Medication.
[a] Worst severity per patient is reported.

treatment naïve subgroup (Table 4).

4. Discussion

The ongoing CLARIFY-MS study aims to assess the effect of cladribine tablets 3.5 mg/kg on HRQoL in patients with highly active RMS, with an interim analysis to evaluate treatment satisfaction, safety, and tolerability. Overall, the results of this pre-planned interim analysis demonstrate that patients reported high treatment satisfaction over 6 months following initiation of treatment (as determined by TSQM), and few SAEs were reported. These findings suggest that cladribine tablets have good treatment efficacy that develops early during Year 1 of administration.

Table 4
Lymphopenia experienced at any time during the first 6 months (safety analysis set).

Patients, n (%)[a]	Treatment naïve $n = 137$	Prior DMT $n = 345$	Total study cohort $n = 482$
Grade ≥2	27 (19.7)	133 (38.6)	160 (33.2)
Grade ≥3	3 (2.2)	30 (8.7)	33 (6.8)
Grade 4	0	0	0
Missing	0	3 (0.9)	3 (0.6)

[a] Patients were categorized using NCI-CTCAE version 5.0 (grade 2, <0.8–0.5 × 10^9/L; grade 3, <0.5–0.2 × 10^9/L; grade 4, <0.2 × 10^9/L), and summarized by worst grade.

In the total study cohort, a mean global satisfaction score of 70.4 ± 18.5 was recorded. In other studies investigating DMT for patients with MS, those who received glatiramer acetate reported a global satisfaction score of 68.7 ± 17.8. In the same study, patients treated with interferon β−1a had a global satisfaction score of 72.4 ± 20.3 (Fernández et al., 2017). A 2019 study found that patients reported a global satisfaction score of 65.1 for teriflunomide in the phase IV Teri-PRO study (Coyle et al., 2019).

Safety results obtained from this population of patients with highly active RMS, including no reports of serious infections, were consistent with the known safety profile of cladribine tablets (Cook et al., 2011, 2019) and provide a good indication of early safety events. Of the four overdose SAEs, two patients from the same site received cladribine tablets in 2 consecutive weeks instead of consecutive months, due to an error in translation of the patient diary. Another patient took the whole of Year 1 treatment in the first week due to a dispensing error, while the remaining patient took an additional tablet during Week 1 of treatment for Year 1 (a dose adjustment was therefore made for Week 2). These overdose events occurred without sequelae. Most observed cases of lymphopenia were of grade 1 or 2. Only 6.8% of the total study cohort had grade 3 lymphopenia and no grade 4 cases were observed. Prior treatment status did not appear to greatly influence safety results, with 59.9% of treatment naïve patients and 55.9% of prior DMT users reporting at least one TEAE. However, the majority of lymphopenia cases were reported in the prior DMT subgroup.

Of note, this is the first study of cladribine tablets to report on use of TSQM v1.4, a simple and validated method of measuring treatment satisfaction (Vermersch et al., 2017). The data obtained from patient-reported outcomes of cladribine tablets treatment through the TSQM v1.4 can therefore supplement the wealth of clinical trial results already reported. However, there are some limitations including the time of the interim analysis – where all patients are 6 months from their first dose of cladribine tablets, and only half of the recommended cumulative dose over 2 years had therefore been administered. This restricts the interpretation of the TSQM effectiveness score and the overall combined score. Nevertheless, it provides evidence of good treatment satisfaction already in the first phase of the treatment cycle. Safety outcomes are also restricted in their interpretation, where adverse events such as severe lymphopenia may become more common following the full recommended cumulative dose. At the close of the CLARIFY-MS trial, TSQM v1.4 results will have been collected at Months 12 and 24 of the study. This will allow for a more accurate interpretation of treatment satisfaction, effectiveness and safety after the full dose of cladribine tablets has been received.

5. Conclusion

In summary, patients reported high satisfaction (TSQM) with cladribine tablets treatment in this pre-planned interim analysis at 6 months. Adverse events reported were consistent with those reported in cladribine tablets pivotal trials, and few SAEs were reported. Most lymphopenia cases were of grade 1 or 2, and there were no instances of grade 4 lymphopenia. The majority of lymphopenia cases were reported in the prior DMT subgroup. These data therefore provide evidence of good tolerability and treatment satisfaction with cladribine tablets both in treatment naïve and DMT-experienced patients during the first phase of the treatment cycle. Data from longer follow-up times will be available at the end of the study to track these outcomes over the full treatment cycle.

Author contributions

All authors contributed to the concept, design, and critical review of the manuscript, and approved the final version for submission

Data availability

Any requests for data by qualified scientific and medical researchers for legitimate research purposes will be subject to Merck Healthcare KGaA's Data Sharing Policy. All requests should be submitted in writing to Merck Healthcare KGaA's data sharing portal https://www.merckgroup.com/en/research/our-approach-to-research-and-development/healthcare/clinical-trials/commitment-responsible-data-sharing.html. When Merck Healthcare KGaA has a co-research, co-development, or co-marketing or co-promotion agreement, or when the product has been out-licensed, the responsibility for disclosure might be dependent on the agreement between parties. Under these circumstances, Merck Healthcare KGaA will endeavor to gain agreement to share data in response to requests.

Declaration of Competing Interest

BB has received consultancy fees, speaker fees, research grants (non-personal), or honoraria from Actelion (Janssen/J&J), Bayer, Biogen, Celgene (BMS), MedDay, Merck Healthcare KGaA, Darmstadt, Germany, Novartis, Roche, Sanofi-Genzyme, and Teva. **RH** has received institutional research grants and fees for lectures and advisory boards from Biogen, Merck Healthcare KGaA, Darmstadt, Germany, and Sanofi-Genzyme. **DL** has participated in speaker bureau for Almirall, Bayer, Biogen, Merck Healthcare KGaA, Darmstadt, Germany, Novartis, Roche, Sanofi-Genzyme, and Teva; has received consultancy fees from Bayer, Biogen, Merck Healthcare KGaA, Darmstadt, Germany, Novartis, and Teva; and has received research grants from Bayer, Biogen, Merck Healthcare KGaA Darmstadt, Germany, and Novartis. **AS** has served on the advisory boards for Merck Healthcare KGaA, Darmstadt, Germany, Novartis, and Sanofi-Genzyme, and has been invited to speak on behalf of Almirall, Biogen, Excemed, Merck Healthcare KGaA, Darmstadt, Germany, and Teva. **FP** has received research grants from Genzyme, Merck Healthcare KGaA, Darmstadt, Germany, and Novartis, and fees for serving as Chair of DMC in clinical trials with Parexel. **JL-S** has accepted travel compensation from Biogen, Merck Healthcare KGaA, Darmstadt, Germany, and Novartis. Her institution receives the honoraria for talks and advisory board commitment as well as research grants from Biogen, Celgene (BMS), Merck Healthcare KGaA, Darmstadt, Germany, Novartis, Roche, Sanofi-Genzyme, and Teva. **XM** has received speaking honoraria and travel expenses for participation in scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past years with Actelion, Alexion, Bayer, Biogen, Celgene (BMS), EMD Serono, Genzyme, Hoffmann-La Roche, Immunic, Janssen Pharmaceuticals, Medday, Merck Healthcare KGaA, Darmstadt, Germany, Mylan, Nervgen, Novartis, Roche, Sanofi-Genzyme, Teva Pharmaceutical, TG Therapeutics, Excemed, MSIF and NMSS. **KS** has received honoraria for speaking, consulting and serving for advisory boards for Biogen, Celgene (BMS), Merck Healthcare KGaA, Darmstadt, Germany, Novartis, Roche, and TG Therapeutics. **MV** has received speaking honoraria and travel expenses for participation in scientific meetings, or participated in advisory boards in the past years with Biogen, Merck Healthcare KGaA, Darmstadt, Germany, Novartis, Roche, Sanofi-Genzyme, and Teva Pharmaceutical. **KR** has received speaking honoraria and travel expenses for participation in scientific meetings, and participated in advisory boards in the past years with Bayer, Biogen, Merck Healthcare KGaA, Darmstadt, Germany, Novartis, Roche, Sanofi-Genzyme, and Teva Pharmaceutical. **EKH** has received honoraria/research support from Actelion (Janssen/J&J), Biogen, Celgene (BMS), Genzyme, Merck Healthcare KGaA, Darmstadt, Germany, Novartis, Roche, and Teva; has served on advisory boards for Actelion (Janssen/J&J), Biogen, Celgene (BMS), Genzyme, Merck Healthcare KGaA, Darmstadt, Germany, Novartis, and Roche; and has been supported by the Czech Ministry of Education, program PROGRES Q27/LF1. **FP** has served on scientific advisory boards for Almirall, Bayer, Biogen, Celgene (BMS), Merck Healthcare KGaA, Darmstadt, Germany, Novartis, Roche, Sanofi-Genzyme, and Teva; he also received speaker honoraria from the same companies and non-personal research grants for his department from Biogen, Merck Healthcare KGaA, Darmstadt, Germany, Novartis, and Sanofi-Genzyme. **NA, AN,** and **BK** are employees of Merck Healthcare KGaA, Darmstadt, Germany.

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