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Original Research Paper

Improvements in quality of life over 2 years with cladribine tablets in people with relapsing multiple sclerosis: The CLARIFY-MS study

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Abstract

Background: Multiple sclerosis (MS) negatively affects health-related quality of life (HRQoL).

Objective: To evaluate HRQoL in people with highly active relapsing MS treated with cladribine tablets (CladT; 3.5 mg/kg cumulative dose over 2 years) in CLARIFY-MS.

Methods: Changes in the MS quality of life (MSQoL)-54 scores were analysed using a repeated mixed-effects linear model. Subgroup analyses were performed for participants who were pretreatment-naïve and those pretreated with disease-modifying therapies (DMTs) before initiating CladT. Safety and tolerability of CladT were also assessed.

Results: MSQoL-54 physical (mean change = 4.86; 95% confidence interval (CI) = 3.18, 6.53) and mental health (4.80; 95% CI = 3.13, 6.46) composite scores (primary endpoints) showed significant improvement at Month 24 versus Baseline ($p < 0.0001$). Changes in the MSQoL-54 scores were consistent across the pretreatment-naïve and DMT-pretreated subgroups. No new severe or opportunistic infections occurred. Most post-baseline lymphopenia events were Grade 1–2 in severity. Transient Grade-3 lymphopenia was observed in 19.7% (95/482) of participants. Grade-4 lymphopenia was not observed.

Conclusions: CladT treatment significantly improved the mean MSQoL-54 physical and mental health composite scores over 2 years. CladT efficacy in HRQoL, relapse rates and Expanded Disability Status Scale scores demonstrates its multidimensional effects in MS treatment.

Keywords: Cladribine tablets, CLARIFY-MS, quality of life, disease-modifying therapies, multiple sclerosis

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Introduction

Many people with multiple sclerosis (PwMS) exhibit a highly active disease course characterised by frequent relapses, magnetic resonance imaging activity and disability progression.[1] The symptoms, disability burden and comorbidities experienced by PwMS have a detrimental effect on their health-related quality of life (HRQoL)[2] and can disrupt their family, social and work lives.[3]

Early initiation of effective treatment may delay disease progression and disability accumulation in people with highly active relapsing MS (RMS).[1,4–6] Cladribine tablets (CladT) at a cumulative dose of 3.5 mg/kg over 2 years is approved for highly active RMS, as defined by clinical and imaging features.[7]

While clinical development programmes for CladT provide valuable information regarding its efficacy and safety,[4,8] its effects on HRQoL and treatment satisfaction were not evaluated as primary or secondary outcomes and have not been explored fully. Analysis of HRQoL data collected during the phase III CLARITY study revealed potential improvements in European Quality of Life-Five Dimensions (EQ-5D) scores; however, data were insufficient to draw clear inferences about outcomes using the disease-specific

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Multiple Sclerosis Quality of Life (MSQoL)-54 instrument.[9]

The CLARIFY-MS study evaluated changes in the HRQoL of people with highly active RMS treated with CladT over 24 months. The 6-month interim analysis from this study demonstrated that CladT was well tolerated and exhibited high treatment satisfaction levels according to the Treatment Satisfaction Questionnaire for Medication (TSQM; version 1.4) scores in both treatment-naïve and disease-modifying therapy (DMT) experienced participants during the first treatment course.[10] Here we report changes in MSQoL-54 physical and mental health composite scores (PCS and MCS) at 24 months from baseline as the primary outcome measure, along with other efficacy and safety findings from CLARIFY-MS.

Participants and methods

Study design

CLARIFY-MS was a 2-year, prospective, open-label, exploratory, single-arm, multicentre, phase IV study (Supplementary Figure S1) conducted at 85 centres across 18 countries between June 2018 and August 2021.

Eligible participants were aged ⩾ 18 years with an Expanded Disability Status Scale (EDSS) score of ⩽ 5.0 and highly active RMS (defined as one relapse in the previous year and ⩾ 1 T1 gadolinium-enhanced lesions or ⩾ 9 T2 lesions while receiving treatment with other DMTs or ⩾ 2 relapses in the previous year regardless of receiving any DMT).[7,10] Detailed inclusion and exclusion criteria have been reported previously.[10] Eligible participants received CladT at a cumulative dose of 3.5 mg/kg over 2 years, with 2 weeks of active treatment per course (Weeks 1 and 5 of each year). Each treatment week comprised 4 or 5 days on which a participant received 10 or 20 mg (one or two tablets) of cladribine as a single daily dose, depending on body weight. The study was completed at the 24-month visit.

The MSQoL-54 instrument is a combination of the 36-Item Short Form Health Survey (SF-36) and 18 additional MS-specific items.[11] Based on expert recommendations, a prespecified improvement of ⩾ 5 points was considered as minimal clinically important difference (MCID) for the SF-36 standardised physical component scale and MSQoL-54 composite scores.

All screening, Baseline, Month 2 and 6 visits were done before the coronavirus disease 2019 (COVID-19) pandemic. For most participants, Month 12 and 12b visits were completed pre-COVID-19, while Month 14 and 18 visits were completed post-COVID-19. All Month 24 visits were completed post-COVID-19 (Supplementary Figure S1). The HRQoL outcomes reported by the participants were collected consistently throughout the study without using any bimodal data collection methods. Patient-reported outcomes (PROs) were completed on hand-held tablet devices, onsite at the clinics.

Endpoints

The primary objective of this study was to assess the HRQoL using the MSQoL-54 instrument in people with highly active RMS treated with CladT over 24 months. The primary endpoints were changes in MSQoL-54 PCS and MCS at 24 months compared with baseline. The secondary objective was to evaluate treatment satisfaction with CladT using the TSQM (version 1.4) at 6 months. The full list of tertiary endpoints has been reported previously.[10] Tertiary endpoints discussed here are changes from baseline in MSQoL-54 PCS and MCS at Month 12 and overall quality of life (QoL) scores at Months 12 and 24; TSQM (version 1.4) global satisfaction scores at Months 12 and 24; TSQM (version 1.4) treatment effectiveness, side effects and convenience scores at Months 6, 12 and 24; annualised relapse rates (ARRs) over 24 months; EDSS scores at Months 6, 12, 18 and 24; 6-month confirmed disability progression (6mCDP); and treatment-emergent adverse events (TEAEs), serious TEAEs and lymphocyte counts gradings (based on National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0)[12] up to Month 24 visit.

Herein, qualifying relapses were required to meet several standard criteria described previously.[10] 6mCDP was defined as an increase in ⩾ 1.5, ⩾ 1 or ⩾ 0.5 points if baseline EDSS scores were 0, 0.5–4.5 (inclusive) or ⩾ 5 points, respectively, confirmed after 6 months.

Statistical analysis

Participants who received ⩾1 dose of CladT were included in the treated set (TS) and were further grouped into two subgroups: those who did not receive any DMTs before CladT treatment (pretreatment-naïve subgroup) and those who received DMTs at any time before CladT treatment (DMT-pretreated subgroup).

Changes in MSQoL-54 composite scores were analysed using a repeated-measures mixed-effects linear

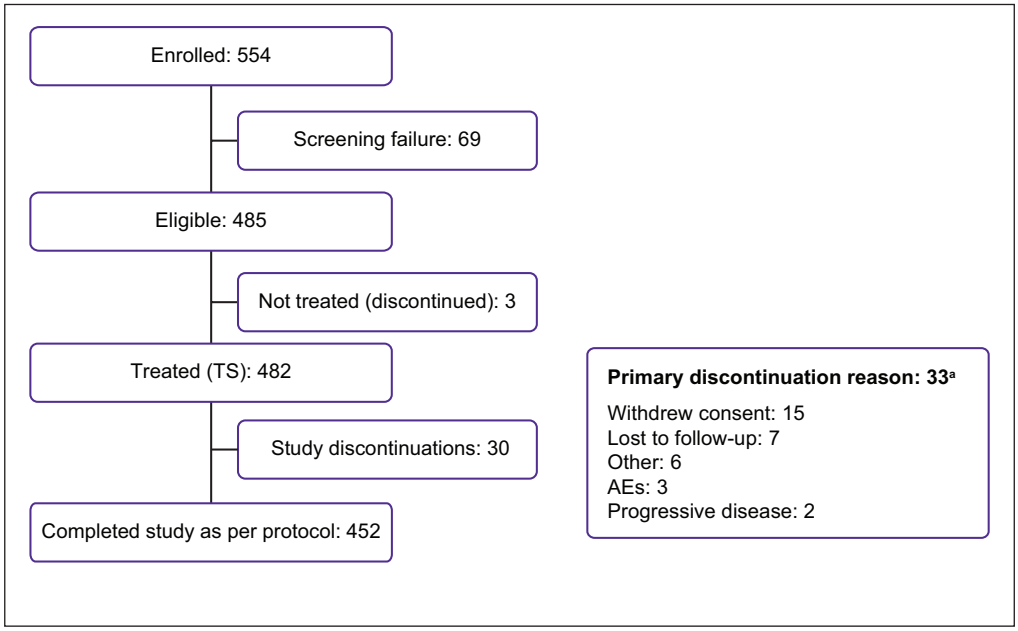


Figure 1. Participant disposition.
AE: adverse event; TS: treated set.
[a]Includes untreated participants.

model that was adjusted for baseline MSQoL-54 composite scores, baseline EDSS scores, age and within-country correlations (pre-planned analyses), along with gender and time since diagnosis (post hoc analyses). In addition, separate post hoc analyses were performed to compare baseline demographics and disease characteristics of participants with and without data available for MSQoL-54 assessments and to evaluate MSQoL-54 subscale data.

The secondary and tertiary endpoints were assessed using methods similar to those used for the primary endpoints, wherever applicable. ARRs were estimated using Poisson regression. Data from the second year of treatment were excluded from the efficacy analyses if a participant delayed their second course of treatment by >3 months. For the analysis of all the secondary and tertiary efficacy endpoints, differences with a p-value of $\leqslant 0.05$ were considered nominally statistically significant as no adjustments for multiple testing were performed. All statistical tests were two-sided with 95% confidence intervals (CIs). Safety data were analysed descriptively.

Results

Participants

Overall, 554 people with highly active RMS were enrolled, 485 of whom met the eligibility criteria. Among them, 482 received $\geqslant 1$ dose of CladT and were included in the TS. In total, 461 participants started the second annual treatment course. Twenty participants had a delay of >3 months in starting the second treatment course owing to lymphopenia ($n=7$) or unknown reasons ($n=13$). In total, 432 participants completed the first and second annual treatment courses, with a treatment compliance of 100% and without a delay of $\geqslant 3$ months in starting the second treatment course. Among the 21 participants who did not start treatment in the second year, 11 discontinued before the Month 12 visit. Finally, 452 participants completed the study at or after Month 24 visit (Figure 1).

Baseline participant demographic and disease characteristics are summarised in Table 1. Participants in the TS had a mean ($\pm$ SD) age of 37.4 ($\pm$ 10.39) years and were predominantly female (70.1%). Overall, the mean ($\pm$ SD) time since the onset of MS was 99.1 ($\pm$ 89.8) months. Most participants (94.1%) experienced one-to-two relapses within the previous 12 months before starting CladT. The mean ($\pm$ SD) MSQoL-54 PCS and MCS for the TS at baseline were 60.2 ($\pm$ 19.7) and 61.2 ($\pm$ 21.7), respectively.

Overall, 348 participants had previous DMT exposure matching the criteria for the DMT-pretreated subgroup, whereas the remaining 134 were included in the pretreatment-naïve subgroup during the analyses.

Table 1. Baseline participant demographic and disease characteristics for the TS.

	Pretreatment-naïve $n=134$	DMT-pretreated $n=348$	Total $N=482$
Mean age ± SD, years	35.2 ± 11.3	38.3 ± 9.9	37.4 ± 10.4
Female, *n* (%)	89 (66.4)	249 (71.6)	338 (70.1)
Mean time since the onset of MS ± SD, months	42.6 ± 58.7	120.9 ± 90.3	99.1 ± 89.8
Mean time since the diagnosis of MS ± SD, months	16.40 ± 32.97	95.62 ± 76.47	73.59 ± 76.04
No. of relapses within 12 months prior to baseline visit, *n* (%)			
0	0 (0.0)	4 (1.1)	4 (0.8)
1	35 (26.1)	225 (64.7)	260 (53.9)
⩾2	99 (73.9)	119 (34.2)	218 (45.2)
EDSS, median (range)	2.0 (0.0–5.0)	2.5 (0.0–5.0)	2.5 (0.0–5.0)
DMT use in prior 6 months to start of study, *n* (%)	0 (0.0)	287 (82.5)	287 (59.5)
MSQoL-54 composite score[a], mean ± SD			
Physical health	62.5 ± 19.7	59.3 ± 19.6	60.2 ± 19.7
Mental health	61.8 ± 21.8	61.0 ± 21.7	61.2 ± 21.7

DMT: disease-modifying therapy; EDSS: Expanded Disability Status Scale; MS: multiple sclerosis; MSQoL-54: Multiple Sclerosis Quality of Life-54 instrument; N: total number of participants; SD: standard deviation; TS: treated set.
[a]Pretreatment-naïve, $n=124$; DMT-pretreated, $n=326$; Total, $N=450$.

The mean time (± SD) since the onset of MS was 42.6 (± 58.7) and 120.9 (± 90.3) months in the pretreatment-naïve and DMT-pretreated subgroups, respectively. The mean MSQoL-54 PCS and MCS were similar in both subgroups at baseline (Table 1). Among the 348 participants who previously received DMTs, 287 (82.5%) received DMTs within 6 months before starting CladT. Most participants switched from interferons (IFNs; $n=84/348$; 24.1%) and dimethyl fumarate ($n=63/348$; 18.1%) to CladT. Other common previous treatments included glatiramer acetate ($n=41/348$; 11.8%), teriflunomide ($n=39/348$; 11.2%) and fingolimod ($n=38/348$; 10.9%).

MSQoL-54 composite scores

Of the 482 participants treated with CladT, 433 were included in the mixed-model analysis of the MSQoL-54 data; as those without MSQoL-54 baseline data or any follow-up assessments ($n=49$) did not have any data available for the analysis. The least squares (LS) mean MSQoL-54 PCS and MCS (primary endpoints) improved significantly at Month 24 by 4.86 (95% CI=3.18, 6.53; $p<0.0001$) and 4.80 (95% CI=3.13, 6.46; $p<0.0001$) points, respectively, versus baseline (Figure 2). In the TS, a change in scores from baseline to the Month 24 visit of ⩾5 points (i.e. a change exceeding the MCID as defined for the study) for MSQoL-54 PCS and MCS was achieved by 47.1% (181/384) and 44.5% (171/384) of participants, respectively. Changes in LS mean MSQoL-54 composite scores were consistent for both subgroups, as indicated by the overlapping CIs for the parameter estimates (Figure 2). Significant improvements in the LS mean MSQoL-54 composite scores were also observed at Month 12 (PCS: 4.45 (95% CI=2.82, 6.08); MCS: 4.67 (3.13, 6.21); both $p<0.0001$); scores at Month 12 were similar to those at Month 24. Baseline demographic and disease characteristics were mostly similar between participants with and without data available for MSQoL-54 analysis (Supplementary Table S1). Owing to technical difficulties in setting up the electronic-PRO functionality in some countries, some participants did not have any MSQoL-54 assessments which contributed to varying distribution of participants across the countries. As expected, the changes in the PCS and MCS were dependent on the respective scores at baseline. The pre-planned analysis showed that participants with high baseline scores tended to exhibit lower PCS and MCS post-baseline, thus demonstrating some regression to the mean. Age and EDSS had marginal impact. Post-baseline scores also tended to be lower for older participants or those with higher EDSS scores at baseline (Supplementary Table S2). A post hoc analysis of the data revealed that time since diagnosis impacted both MSQoL-54 MCS and PCS, whereas gender had no predictive value on either composite score (Supplementary Table S3).

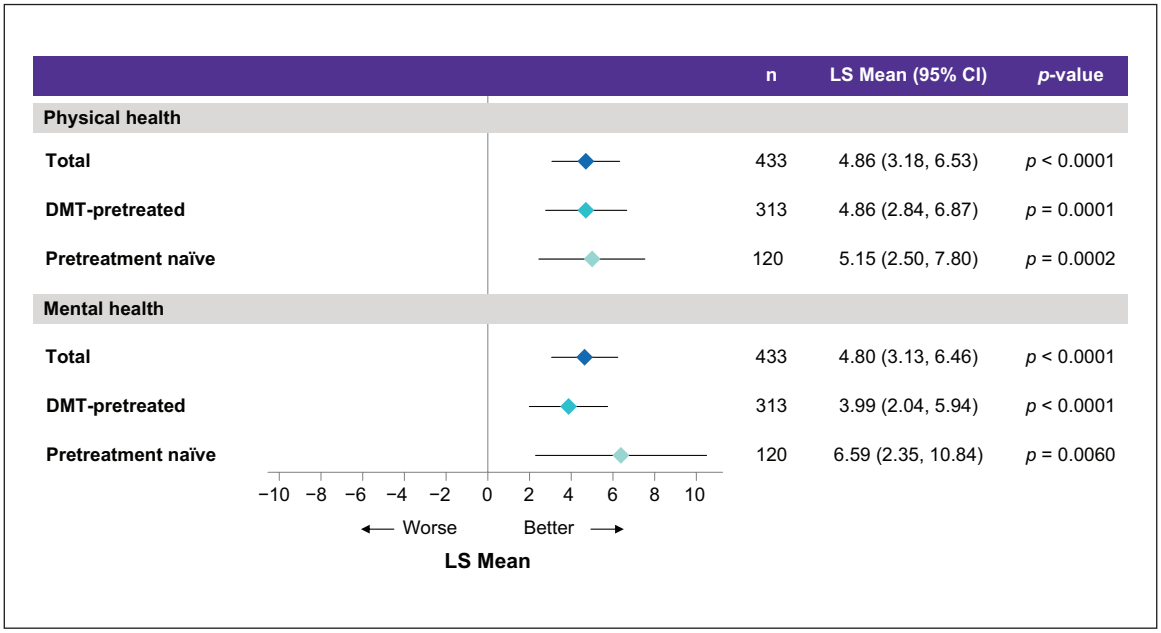


Figure 2. MSQoL-54 PCS and MCS: change from baseline to the Month 24 according to the subgroups in the TS.
CI: confidence interval; DMT: disease-modifying therapy; LS: least squares; MCS: mental health composite score; MSQoL-54: multiple Sclerosis Quality of Life-54 instrument; PCS: physical health composite score; TS: treated set.
Error bars indicate CIs.

MSQoL-54 overall QoL and individual subscale scores

The LS mean MSQoL-54 overall QoL scores improved significantly by 2.71 (95% CI = 1.32, 4.10; $p = 0.0001$) and 2.88 (95% CI = 1.41, 4.34; $p = 0.0001$) points at Months 12 and 24, respectively, versus baseline. A post hoc analysis of the individual MSQoL-54 subscale scores showed improvements at Months 12 and 24 (versus baseline) across most MSQoL-54 subscales. The highest changes in LS mean MSQoL-54 scores from baseline to Month 24 were observed for role limitations owing to physical problems (12.19; 95% CI = 8.78, 15.60), health distress (9.09; 95% CI = 6.42, 11.76) and emotional problems (6.97; 95% CI = 1.68, 12.26) (Figure 3).

TSQM

The 6-month LS mean TSQM (version 1.4) global satisfaction score (secondary endpoint) was 72.02 (95% CI = 68.76, 75.28). The LS mean global satisfaction, effectiveness, side effects and convenience scores remained similar across Months 6, 12 and 24 (Supplementary Figure S2).

Qualifying relapse/ARR

The estimated ARRs of the qualifying relapses were 0.13 (95% CI = 0.11, 0.16), 0.08 (95% CI = 0.05, 0.13) and 0.15 (95% CI = 0.12, 0.18) in the TS, pretreatment-naïve and DMT-pretreated subgroups, respectively. In the TS, 91/482 participants (18.9%; pretreatment-naïve: 21/134, 15.7%; DMT-pretreated: 70/348, 20.1%) experienced a qualifying relapse during the study. Overall, 83 participants (17.2%; pretreatment-naïve: $n = 19/134$, 14.2%; DMT-pretreated: $n = 64/348$, 18.4%) with ⩾1 qualifying relapse required steroid treatment, whereas 24 participants (5.0%; pretreatment-naïve: 6/134, 4.5%; DMT-pretreated: 18/348, 5.2%) with ⩾1 qualifying relapse required hospitalisation.

EDSS and 6mCDP

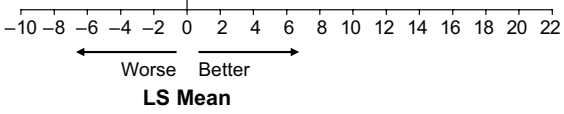
The median EDSS score at all the timepoints was 2.5 for the TS and DMT-pretreated subgroup, and 2.0 for the pretreatment-naïve subgroup (Supplementary Figure S3). During the treatment period, most participants in the TS (88.0%; 424/482), pretreatment-naïve (88.1%; 118/134) and DMT-pretreated (87.9%; 306/348) subgroups were free from 6mCDP.

Safety

Of the 482 participants in the TS, 376 (78.0%) experienced ⩾1 TEAE after starting CladT (Table 2). The most common TEAEs were headache (21.8%; 105/482 participants), lymphopenia (15.1%; 73/482

Physical health

Scales and composite score	n	LS mean (95% CI)	*p*-value
Physical health composite score			
Month 12	433	4.45 (2.82, 6.08)	$p = 0.0001$
Month 24	433	4.86 (3.18, 6.53)	$p < 0.0001$
Physical health			
Month 12	433	2.77 (0.74, 4.80)	$p = 0.0115$
Month 24	433	2.17 (0.03, 4.30)	$p = 0.0474$
Role limitations due to physical problems			
Month 12	433	8.98 (5.67, 12.28)	$p < 0.0001$
Month 24	433	12.19 (8.78, 15.60)	$p < 0.0001$
Pain			
Month 12	433	3.27 (0.74, 5.80)	$p = 0.0154$
Month 24	433	3.56 (0.99, 6.12)	$p = 0.0101$
Energy			
Month 12	433	3.99 (2.46, 5.53)	$p < 0.0001$
Month 24	433	3.86 (2.25, 5.47)	$p < 0.0001$
Health perception			
Month 12	433	3.42 (2.04, 4.79)	$p < 0.0001$
Month 24	433	4.91 (3.40, 6.43)	$p < 0.0001$
Social function			
Month 12	433	4.37 (1.97, 6.77)	$p = 0.0016$
Month 24	433	4.00 (1.58, 6.42)	$p = 0.0031$
Health distress			
Month 12	433	8.97 (6.35, 11.59)	$p < 0.0001$
Month 24	433	9.09 (6.42, 11.76)	$p < 0.0001$
Sexual function			
Month 12	433	0.82 (–2.49, 4.12)	$p = 0.6025$
Month 24	433	0.11 (–3.23, 3.45)	$p = 0.9451$



Mental health

Scales and composite score	n	LS mean (95% CI)	*p*-value
Mental health composite score			
Month 12	433	4.67 (3.13, 6.21)	$p < 0.0001$
Month 24	433	4.80 (3.13, 6.46)	$p < 0.0001$
Role limitations due to emotional problems			
Month 12	433	6.29 (1.13, 11.45)	$p = 0.0213$
Month 24	433	6.97 (1.68, 12.26)	$p = 0.0135$
Emotional well-being			
Month 12	433	3.56 (1.42, 5.70)	$p = 0.0039$
Month 24	433	3.28 (1.08, 5.48)	$p = 0.0067$
Cognitive function			
Month 12	433	2.20 (–0.18, 4.59)	$p = 0.0662$
Month 24	433	2.75 (0.34, 5.17)	$p = 0.0295$
Health distress			
Month 12	433	8.97 (6.35, 11.59)	$p < 0.0001$
Month 24	433	9.09 (6.42, 11.76)	$p < 0.0001$
Overall quality of life			
Month 12	433	2.71 (1.32, 4.10)	$p = 0.0001$
Month 24	433	2.88 (1.41, 4.34)	$p = 0.0001$

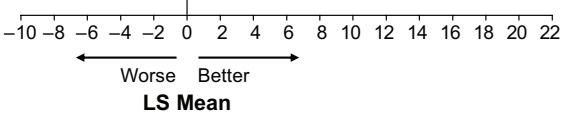


Figure 3. Changes from baseline for each MSQoL-54 scale and composite score for the TS.
CI: confidence interval; LS: least squares; MSQoL-54: multiple Sclerosis Quality of Life-54 instrument; TS: treated set.
Error bars indicate CIs.

Table 2. Summary of TEAEs in the TS.

No. of participants with:	Pretreatment-naïve *n* = 134 *n* (%)	DMT-pretreated *n* = 348 *n* (%)	Total *N* = 482 *n* (%)
Any TEAE[a]	109 (81.3)	267 (76.7)	376 (78.0)
Mild	55 (41.0)	136 (39.1)	191 (39.6)
Moderate	47 (35.1)	122 (35.1)	169 (35.1)
Severe	7 (5.2)	9 (2.6)	16 (3.3)
Any study treatment–related TEAE[a]	53 (39.6)	137 (39.4)	190 (39.4)
Mild	33 (24.6)	67 (19.3)	100 (20.7)
Moderate	17 (12.7)	66 (19.0)	83 (17.2)
Severe	3 (2.2)	4 (1.1)	7 (1.5)
Any serious TEAE	8 (6.0)	18 (5.2)	26 (5.4)
Any study treatment–related serious TEAE	2 (1.5)	3 (0.9)	5 (1.0)
Any TEAE leading to permanent discontinuation of the study treatment	1 (0.7)	8 (2.3)	9 (1.9)
TEAEs observed in > 4% of the total population[b]			
Headache	29 (21.6)	76 (21.8)	105 (21.8)
Lymphopenia	13 (9.7)	60 (17.2)	73 (15.1)
Nasopharyngitis	27 (20.1)	38 (10.9)	65 (13.5)
Upper respiratory tract infection	17 (12.7)	30 (8.6)	47 (9.8)
Urinary tract infection	12 (9.0)	27 (7.8)	39 (8.1)
Back pain	12 (9.0)	26 (7.5)	38 (7.9)
Fatigue	13 (9.7)	17 (4.9)	30 (6.2)
Influenza	9 (6.7)	20 (5.7)	29 (6.0)
Pain in extremity	12 (9.0)	14 (4.0)	26 (5.4)
Nausea	9 (6.7)	16 (4.6)	25 (5.2)
Oral herpes	6 (4.5)	19 (5.5)	25 (5.2)
Bronchitis	6 (4.5)	17 (4.9)	23 (4.8)
Arthralgia	9 (6.7)	11 (3.2)	20 (4.1)

DMT: disease-modifying therapy; MedDRA: Medical dictionary for Regulatory Activities; TEAE: treatment-emergent adverse event; TS: treated set.
[a]Worst severity per participant was reported.
[b]MedDRA version 24.0.

participants) and nasopharyngitis (13.5%; 65/482 participants). Overall, 3.1% (15/482) participants experienced COVID-19-associated TEAEs. Most participants experienced mild (39.6%; 191/482) or moderate (35.1%; 169/482) TEAEs. Severe TEAEs were observed in 3.3% (16/482) participants.

Serious TEAEs (Supplementary Table S4) were observed in 26/482 (5.4%) participants, of which 5 (1.0%) were reported to be potentially related to the study treatment (overdose, $n = 3$; cervical dysplasia, $n = 1$; upper respiratory tract infection, $n = 1$).

Nine out of 482 (1.9%) participants permanently discontinued study treatment due to TEAEs. No deaths were reported during this study.

As per the laboratory assessments, most post-baseline lymphopenia events were Grade 1–2 in severity. Transient Grade-3 lymphopenia was observed in 19.7% (95/482) of participants. No cases of Grade-4 lymphopenia were observed. Frequency of Grade-3 lymphopenia was higher in the DMT-pretreated subgroup (23.0%; 80/348) than the pretreatment-naïve subgroup (11.2%; 15/134) (Figure 4).

Discussion

The CLARIFY-MS study assessed changes in HRQoL of participants treated with CladT 3.5 mg/kg over 24 months. The mean MSQoL-54 PCS and MCS scores at Month 24 improved significantly from baseline. ARRs of the qualifying relapses in CLARIFY-MS

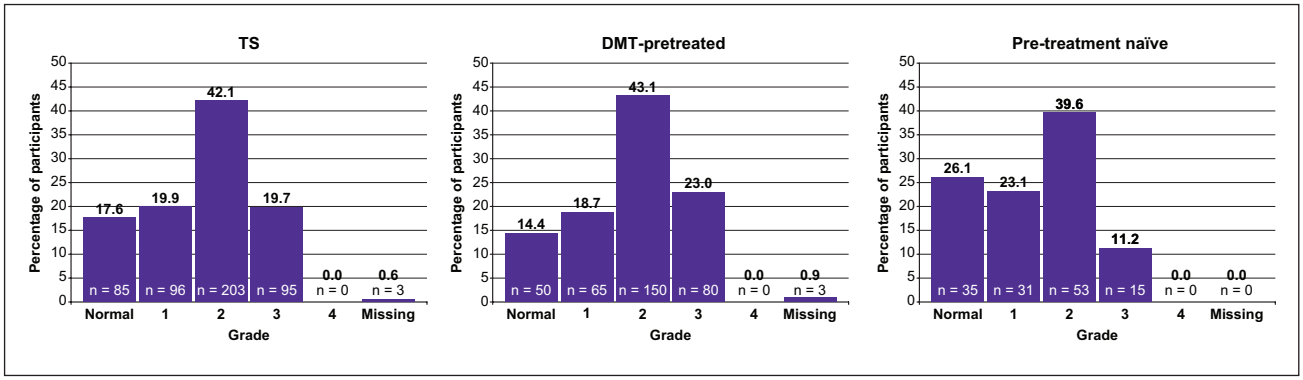


Figure 4. Highest post-baseline grade of lymphopenia.
DMT: disease-modifying therapy; NCI-CTCAE: National Cancer Institute-Common Criteria for Adverse Events; TS: treated set.
Absolute lymphocyte count grading was done based on NCI-CTCAE version 5.0.
TS, $N = 482$; DMT-pretreated, $n = 348$; pretreatment-naïve, $n = 134$.

were comparable with those reported by the phase III CLARITY study;[4] median EDSS scores remained stable throughout this study. No new safety signals were revealed; in particular, there were no new severe or opportunistic infections. These data from CLARIFY-MS supplement the extensively published clinical trial findings regarding the efficacy and safety of CladT,[4,8] while substantially enhancing our understanding of the effect of CladT on the participants' HRQoL.

HRQoL assessment provides essential information regarding the possible benefits and risks of DMTs beyond the clinician-reported outcomes.[11,13] Measuring HRQoL and other PROs can increase awareness of clinicians regarding the concerns and priorities of patients, ultimately enhancing shared decision-making and patient-centred care.[11,14] HRQoL improvement is a key component of drug efficacy in MS.[15] Findings from small randomised controlled trials and observational studies involving PwMS indicate that treatment with DMTs is linked to either prevention of worsening, stabilisation or improvement of HRQoL.[11] However, limited prospective data are available regarding HRQoL in large trials involving PwMS, particularly with regard to disease-specific measures. In the phase IV EPOC study, PwMS who switched from injectable platform therapies (glatiramer acetate and IFNs) to fingolimod exhibited higher SF-36 PCS and MCS compared with the PCS of those continuing therapy with IFN-β1b and IFN-β1a.[16,17] The HRQoL data from the phase III CARE-MS I and II studies showed that more PwMS who received alemtuzumab recorded improvements in the SF-36 PCS than those who received IFN-β1a.[18] In the phase III OPERA-II study, the PwMS who received ocrelizumab demonstrated a greater adjusted mean change in the SF-36 PCS scores from baseline than those who received IFN-β1a.[19] These findings indicate that high-efficacy therapies are linked to greater improvements in HRQoL than platform therapies in PwMS. In the CLARIFY-MS study, CladT significantly improved the MSQoL-54 PCS and MCS over 2 years, but in a dedicated HRQoL study in a cohort with highly active RMS, using a disease-specific scale.

Despite the growing interest in exploring HRQoL-related endpoints in clinical studies, their subjective nature and potential for large inter-individual variation renders it difficult to interpret the clinical relevance of such changes. MCID sets a threshold value for changes in a scale or instrument considered clinically relevant.[11,20–22] Several studies have selected changes of 0.5 times the SD for HRQoL scores as clinically relevant.[11,21,23] Based on these findings and expert recommendations, the MCID was defined (from baseline to Week 24) as $\geqslant 5$ for the MSQoL-54 MCS and PCS in our study. Notably, $>40\%$ participants in CLARIFY-MS achieved an MCID of $\geqslant 5$ points for the MSQoL-54 PCS and MCS. The HRQoL benefits of CladT observed in the CLARIFY-MS study confirm and expand the initial HRQoL EQ-5D and MSQoL-54 instrument findings of the CLARITY study.[9]

In PwMS, higher treatment satisfaction is typically linked to fewer relapses, lower disability scores and increases in HRQoL.[24,25] Data from the cross-sectional, observational, multicentre THEPAMS study in PwMS treated with DMTs showed that the mean SF-36 PCS

and MCS were significantly higher in those with high treatment satisfaction scores (TSQM global score ⩾ 75) versus those being less satisfied (TSQM global score < 75; all $p < 0.001$).[24] The current analysis allowed us to assess treatment satisfaction over a longer period after the full course of CladT treatment. The high treatment satisfaction reported in the pre-planned interim analysis of the CLARIFY-MS data at Month 6[10] was maintained over 2 years, which may have been linked to the overall improvements in QoL.

The MSQoL-54 subscale data from CLARIFY-MS show that CladT acts on multiple individual domains of HRQoL to bring about holistic improvements in overall QoL of people with highly active RMS. Hence, the participants experienced improvements across multiple physical health domains, including physical function, limitations due to physical problems, pain, energy levels, social function and health perception. Similarly, improvements in role limitations due to emotional problems, emotional well-being, cognitive function and health distress domains contributed to the overall improvement in mental health.

Study limitations

As CLARIFY-MS was a single-arm study, there was no control group to compare with the treated group. Results for each timepoint were compared to baseline values, wherever applicable. As this was an open-label study, the participants and investigators possessed prior knowledge regarding the study treatment, which may have influenced certain responses of participants to questions in the MSQoL-54 instrument and TSQM (version 1.4), and observations made by the investigators.

Conclusions

CladT treatment significantly improved the MSQoL-54 PCS and MCS with a substantial proportion of participants achieving clinically relevant improvements in HRQoL over 2 years. The ARRs and EDSS data in this study were in accordance with the findings of randomised controlled trials in the CladT clinical development programme. No new safety signals impacting the established benefit-to-risk profile of CladT in people with highly active RMS were observed. CladT efficacy in QoL, relapse rates and EDSS scores demonstrates its multidimensional effects in MS treatment.

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Declaration of Conflicting Interests

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Ethical Approval

The study was conducted in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki. The Institutional Review Board or ethics committee for each trial site approved the protocol.

Consent to Participate

Written informed consent was obtained from all participants before initiating any study-related procedures.

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Supplemental Material

Supplemental material for this article is available online.

Data Availability Statement

Any requests for data by qualified scientific and medical researchers for legitimate research purposes will be subject to Merck's Data Sharing Policy. All requests should be submitted in writing to Merck'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 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 will endeavour to gain agreement to share data in response to requests.

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