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Positive impact of cladribine on quality of life in people with relapsing multiple sclerosis

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ABSTRACT

Background: A number of elements of the pivotal oral cladribine (CLARITY) trial are unpublished.

Objective: To report the impact of cladribine on health-related quality of life (QoL) in people with relapsing multiple sclerosis (pwRMS).

Methods: QoL data from the phase III trial of two different doses (3.5mg/kg and 5.15mg/kg) of oral cladribine in pwRMS were acquired from the European Medicines Agency through Freedom of Information. Spearman's rank correlation was used to analyse the relationship between baseline QoL scores and baseline Expanded Disability Status Scale (EDSS) scores. Responses the Euro Quality of Life 5 dimension (EQ5D) and Multiple Sclerosis Quality of Life 54 (MSQOL54) questionnaires were compared between treatment and control groups using univariate analyses of covariance.

Results: In total n= 5,148 EQ5D responses and n= 894 MSQOL54 physical, mental-health and dimension scores were extracted. Baseline EQ5D indices correlated with EDSS scores. After two years, pwRMS taking 3.5mg/kg (p=0.001) and 5.25mg/kg (p=0.022) reported significantly improved EQ5D index scores compared with placebo. Positive, yet non-significant, differences were detected in MSQOL54 scores between cladribine and placebo.

Conclusion: Analysis of the CLARITY dataset suggests that, over and above its established clinical efficacy, cladribine leads to improved QoL over 96 weeks. ClinicalTrials.gov identifier, NCT00213135

INTRODUCTION

Multiple sclerosis (MS) is a major demyelinating and neurodegenerative disease resulting in the accumulation of disability and significant loss of Quality of Life (QoL) to the affected individual and their carers[1,2]. QoL may be retained or improved by use of effective disease modifying treatments (DMT) that stop or slow the accumulation of disability[3].

Cladribine is a deoxyadenosine analogue, which is phosphorylated to 2-chlorodeoxyadenosine triphosphate that is selectively cytotoxic for lymphocytes in humans[4,5]. Cladribine has activity as an injectable, generic agent[6] or as an oral pro-drug[5,7]. This was particularly well demonstrated in the phase III "Cladribine tablets treating multiple sclerosis orally "(CLARITY) trial, where cladribine markedly inhibited (i) lesion accumulation as detected on magnetic resonance imaging (MRI); (ii) relapses and (iii) three month-sustained disability progression[5,7]. For a number of reasons, including a perceived increase in cancer risk[5], and in the absence of additional trial data, the regulators rejected license applications prompting the manufacturer of oral cladribine to halt their programme for commercial development of the drug in 2011 [8]. Following resubmission in 2015, however, the Committee for Medicinal Products for Human Use of the European Medicines Agency (EMA) has now adopted a positive opinion with licensing of oral cladribine (Mavenclad®) likely in the 3rd quarter 2017 (http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/004230/WC500229786.pdf).

Based on meeting abstracts prior to 2011, the termination of the oral cladribine programme meant a significant cache of data gathered during CLARITY never underwent peer- reviewed publication. Given the excellent efficacy of cladribine demonstrated in people with relapsing MS (pwRMS)[5], as well as people with a first demyelinating event suggestive of MS[9], and following a meta-analysis suggesting the cladribine-associated cancer frequency was no different to natural aging or that found in pivotal trials of other MS-DMT[10], we saw a future in developing cladribine for people with MS further[11,12]. We therefore obtained the entire CLARITY dataset using a Freedom of Information (FoI) request to the EMA, which included data on health-related QoL.

As QoL indices are particularly sensitive to fatigue, cognitive impairment, emotional changes and social isolation[13,14], they enable a complementary assessment of the impact of DMT over and above clinical scales, such as the expanded disability status score (EDSS) scale, which suffers from bias, notably due to the dominant contribution of ambulation at scores between 3.5 and 8[15]. Furthermore, QoL indices may be more sensitive to adverse effects of treatments[16,17]. Given the

efficacy of cladribine to inhibit relapsing disease[5-7], we hypothesised a positive impact on QoL in pwRMS.

MATERIALS & METHODS

Trial Registration and data acquisition

After the apparent termination of the commercial development of oral cladribine in 2011, and subsequent discussions with the UK Medicines and Healthcare products Regulatory Agency about approaches to develop generic cladribine, the full regulatory submission of the 96 week CLARITY trial (NCT00213135)[5] was obtained through FoI request to the EMA (submitted May 2013; obtained November 2013). Whilst the original trial was undertaken following R&D approval and pwRMS recruited after informed consent[5], no R&D approval was required to use the "public domain" documents used for the current analysis of anonymised datasets. Information regarding study design, setting, participants, eligibility, variables, randomization, blinding, study size, bias reduction, flow diagrams of participants and the CONSORT and STROBE reporting guidelines can be obtained from the original trial publication[5].

The dataset from the EMA was provided in portable document format (pdf). Files containing relevant data were identified and converted into Microsoft Excel spreadsheets using a pdf parser developed on a Python 2.7 platform at the MidPlus computational facilities at Queen Mary University of London (code available on request). The converted data was validated by comparing sample records between pdf and spreadsheet versions of the files. Scores listed as "unscheduled" or "99999" were excluded from analysis.

Trial Design

The full details of the trials have been reported previously[5]. Briefly, 1326 pwRMS were randomized 1:1:1 (n=1184 completed the 96 week study) to receive either placebo (n=437; n=380 completed), or one of two doses of oral cladribine pro-drug. Patients were given tablets containing either 10mg/day (60-69.9kg body weight) or 20mg/day (70-79kg body weight) cladribine administered for 4-5 days in weeks 0 and 5 (year 1) and weeks 48 and 52 (year 2) to result in a total cumulative dose of 3.5mg/kg (n=433. n=398 completed). Those randomized to the 5.25mg/kg arm were given additional doses in weeks 9 and 13 (n=456; n=406 completed)[5]. Clinical efficacy was comparable for both doses of cladribine[5,7]. QoL scores were collected at baseline and at weeks 24, 48, 72 and 96.

Quality of Life indices

The regulatory submission included the EuroQol five dimension three level (EQD5-3L)[18] and the Multiple Sclerosis Quality of Life-54 (MSQOL-54)[1,19] questionnaires.

The EQ5D-3L, a self-completed questionnaire, addresses five distinct dimensions, (i) mobility, (ii) self-care, (iii) usual activities, (iv) pain or discomfort and (v) anxiety, where participants had a choice of three responses per dimension: no problems, moderate problems or severe problems[18]. A scoring algorithm was implemented to convert responses into a summary index, known as the EQ5D index[18], where 1 represents the best QoL. Values below 0 were not excluded. Values marked on a self-rating Visual Analogue Scale (VAS), known as EQ5D-VAS, were also collected. EQ5D-VAS scores on a scale 0-100, where 0 represented the worst QoL. The EQ5D was collected at baseline and at weeks 24, 48, 72 and 96.

The MSQOL-54 is a fifty-four item questionnaire that measures twelve domains: physical function, role limitations-physical, role limitations-emotional, pain, emotional well-being, energy, health perceptions, social function, cognitive function, health distress, overall QoL, and sexual function[1]. Subscale and summary scores were calculated as described previously[19]. For each domain, relevant item scores were totalled and then divided by the number of completed responses. This gave a score for each of the twelve domains. Physical-health (PHS) and mental-health (MHS) component scores were calculated from weighting relevant domains and summing the resultant products. Male and female sexual function domain scores were added together to provide a single physical component summary score. The MSQOL-54 scores ranged between 0 and 100 where 100 represented the highest quality of life. Changes from baseline scores were calculated for each time point. The MSQOL-54 was collected at baseline and at weeks 24, 48, 72, 96.

Statistical Analysis

The relationship between baseline QoL scores and baseline EDSS was assessed using Spearman's rank correlation. Univariate analyses of covariance (ANCOVA) tests, adjusted for baseline score, age at baseline, centre, ethnic group, and gender were conducted to compare mean QoL scores at baseline, and at weeks 24, 48, 72 and 96. This method was in line with EMA guidelines[20] and similar to those used in previous QoL studies[21, 22]. The impact of relapses on QoL was also assessed using ANCOVA analysis, comparing pwRMS who had a relapse, requiring steroid use as a reflection of the severity, between treatment and placebo-control groups. Relapses listed as "unscheduled" were not included as relapses up to week 48, because it could not be safely assumed that these relapses

occurred during this time. However, all relapses including those listed as "unscheduled" were included as relapses up to week 96 and were totalled for each treatment arm. To investigate whether changes in EQ5D index were independent of relapse reduction, two linear regression models were compared. The first model set high dose, low dose groups and their baseline index scores as predictors for changes in EQ5D index at week 96. The second model also adjusted for whether participants relapsed at any point during the trial (a binary variable).

Changes in EQ5D were examined using the index of "minimal clinically important difference" (MCID)[23], defined as the smallest QoL change that pwRMS considered important. This is because changes greater than the MCID are more likely to translate to real-world patient benefit[24]. Previously, based on data from the North American Research Committee on Multiple Sclerosis (NARCOMS) registry the EQ5D-3L MCID was between 0.050 and 0.084[23]The likelihood that a patient experienced a QoL change greater than the MCID, set at 0.08, was assessed using a logistic regression model. The covariates were high, low dose groups and index scores at baseline. The dependent variable was whether or not individuals achieved a MCID in change EQ5D index. The sample population came from the entire trial period (from week 24 to week 96). All statistical analysis was performed using SPSS version 23. No imputation was made for missing data.

RESULTS

Analysis of respondent demography showed that the age and the gender ratio in the respondent sample matched the overall demography of the CLARITY trial[3], with no significant imbalances between treatment groups (Supplementary data. Table S1). At baseline pwRMS with higher EDSS scores had a lower EQ5D index (r_s= -0.472, n= 430, p< 0.001) and EQ5D VAS score (r_s=-0.442, n= 434, p< 0.001).

Effect of cladribine on EQ5D Index

At baseline, differences in EQ5D-index and EQ5D-VAS scores between groups were not statistically significant. Participants receiving placebo experienced worsening in mean QoL over the duration of the trial reaching the lowest point by week 96 (Figure 1). In weeks 24, 72 and 96 the mean index change between groups was significantly different. In week 24, (F[2, 950] = 5.514, p=0.004), participants treated with the low dose of cladribine had significantly higher index scores compared with placebo, likewise for the high dose of cladribine, (p= 0.014 for low-dose, p= 0.003 for high-dose). In week 72, only the low dose cladribine group had significantly higher scores compared with placebo (F[2, 899] = 4.340, p=0.013), p= 0.003 for low dose). Finally in week 96, (F[2, 945] = 5.639, p=0.004), participants treated with either dose of cladribine had significantly higher EQ5D index scores compared to placebo (planned contrast analysis; p= 0.001 for low-dose, p= 0.022 for high-dose).

Impact of cladribine on EQ5D VAS

Whilst the 3.5mg/kg cladribine group experienced consistent improvement in mean VAS scores throughout the trial, the placebo group reported worse than baseline VAS scores throughout the trial. However, none of these differences were statistically significant at any time point over the duration of the trial (Table S1).

Impact of cladribine on EQ5D index after relapse

An ANCOVA adjusted for: age, gender, centre, baseline score, ethnicity and treatment group was used to assess the impact of relapses on the mean observed EQ5D index and VAS scores. This analysis was performed on scores reported by pwRMS at the end of weeks 48 and 96. The analysis showed that EQ5D-VAS scores in pwRMS who had at least one relapse up to week 48, (M = 0.60, SD = 0.21) was significantly lower than in patients who did not relapse (M = 0.71, SD = 0.21; F(1, 923) = 19.178, p < 0.001). Similarly, pwMS who relapsed by week 48 of the trial (M = 0.63, SD = 0.26) had

significantly lower EQ5D index scores compared with pwMS who did not relapse (*M = 0.73, SD = 0.22*; *F(1, 913) = 13.440, p < 0.001).*Similarly, participants who relapsed by week 96 also had a significantly lower EQ5D Index compared to non-relapsed participants (0.60 vs. 0.73; *F(1, 945) = 29.052, p* < 0.001). This effect was also evident for EQ5D-VAS scores up to week 96, (0.61 vs. 0.71; *F*[1, 956] = 29.644, *p* < 0.001), suggesting that relapses had a detrimental effect on QoL.

ANCOVA adjusted for: age, gender, centre, baseline score and ethnicity was also used to assess the impact of cladribine on QoL scores in pwRMS experiencing a relapse. There was no statistically significant difference in EQ5D Index between groups within those who relapsed at week 48 or week 96. However, there were differences in the EQ5D VAS(*F*[2, 101] = 3.124, *p* = 0.048). The VAS score was significantly greater (better QoL) in relapsed placebo patients (*M* = 0.62, *SD* = 0.22) compared with relapsed low dose patients (*M* = 0.52, *SD* = 0.20; planned contrast analysis *p* = 0.039). Thus, if they had a relapse, pwRMS treated with cladribine had no better QoL compared to pwRMS on placebo.

Two linear regression models were compared to explore the influence of relapse reduction on changes in QoL further. The first model, which set doses and baseline scores as independent variables, showed that both high (p=0.028) and low dose (p=0.001) groups were significantly higher than placebo at Week 96. However, when relapses up to week 96 were added as another independent variable in a second regression model, the high dose improvement was reduced and no longer significant (p=0.161). The low dose effect remained significant (p=0.016) even after adjustment for relapses.

Impact of cladribine on EQ5D dimensions

The proportion of pwRMS reporting at least one point increase at week 96, which indicated worsening of their EQ5D dimensions was compared between treatment and control groups (Table 1). It was found that only the self-care dimension reached significance (P<0.01) for both of the cladribine treatment groups (Table 1). Furthermore a larger proportion of pwRMS on placebo worsened in mobility and anxiety dimensions compared with people treated with cladribine (Chi square; mobility: χ^2 = 7.911, p= 0.019 [2d.f. n= 964]; self-care: χ^2 = 7.104, p= 0.029 [2d.f. n= 964], anxiety: χ^2 = 6.389, p = 0.041 [2d.f. n=964]).

Impact of cladribine on pwRMS reporting a MCID in EQ5D

Proportions of pwRMS achieving MCID in their EQ5D index score change at each time point are detailed in table 2. Our logistic model (χ^2 = 368.7 p< 0.001 [3d.f. n= 4076]) showed that Individuals

on a low dose had an odds ratio of 1.26 (p=0.019) compared to placebo. Those on high dose had an odds ratio of 1.06 (not statistically significant).

Impact of cladribine on MSQOL54 scores

The number of MSQOL-54 responses was small (n=45-73). Baseline MSQOL54 physical and mental health component scores between groups were not significantly different (Supplementary data. Table S2). Univariate ANCOVA analyses adjusted for baseline score, age gender, centre and ethnicity were conducted at each time point to assess the impact of oral cladribine on MSQOL-54 physical and mental health component scores failed to show significant improvements compared to placebo (Supplementary data. Table S2) at any point.

DISCUSSION

Following refusal by the EMA to license oral cladribine in 2011, the drug was withdrawn from markets, where it had been licensed (Russia, Australia), and ongoing trials were terminated[8,9]. However, the high efficacy and modest adverse effect profile of cladribine in pwRMS[5,7,10] led us to seek information that could help inform on the merits of preparations other than the one used in CLARITY. Parenteral cladribine, which is available as a generic drug for treatment of people with hairy cell leukaemia, may have benefits for personalized dosing due to its consistent bioavailability of 100% compared to the oral route with a mean of 42% bioavailability[25] prompting a study exploring combination of the acid sensitive oral cladribine pro-drug with the proton pump inhibitor pantoprazole (NCT00938366; the study has yet to be reported). However, a successful FoI request to the EMA for documentation placed in the public domain in 2009 enabled us to independently analyse the trial data. Here, we present class II evidence that cladribine has QoL benefits in addition to the clinical benefits previously reported[5,7,9].

The key result of this analysis is that cladribine, at both doses used in CLARITY, 3.5mg/kg and 5.25mg/kg orally[5], significantly improved QoL as measured using the widely accepted EQ5D index. The benefits in EQ5D for pwRMS treated with both doses was particularly significant for self-care, although influences on mobility could be detected and may be related to the clinical efficacy of cladribine in reducing relapses and delaying progression[5,7]. It is plausible these clinical effects also translate into reduced anxiety.

The data collected during CLARITY are in line with previous studies suggesting that relapses have a significant impact on QoL[16,26]. The implication from linear regression is that the beneficial effect on QoL using the higher dose was mediated by the relapse-reducing effect of cladribine, whereas at the lower dose cladribine may also lead to improved QoL independent of its relapse-reducing effect. Given there was no difference in efficacy between the two doses during CLARITY, we hypothesize the lower incidence of adverse effects in the low dose group as the potential cause for the "relapse-independent" QoL benefit on the lower dose.

The magnitude of QoL benefits was sufficiently robust to reflect in the MCID, suggesting improved QoL was noticeable at the level of the individual patient. Whilst the EQ5D-VAS score change was consistent with the EQ5D, differences between groups were small and did not reach statistical significance. The reason for this may be the lower sensitivity of this QoL index, where there may be

issues with completion and coding implementation and where health improvements are less likely to be reported[27]. Furthermore, no difference was detected using the MSQOL-54, likely due to the small number of respondents not providing a statistically meaningful sample.

Given only few fully-blinded head-to-head studies have been undertaken so far, it is difficult to compare QoL indices between different interventions for pwRMS directly. Not all DMT have had an impact on QoL indices[28, 29], however improvements have been detected with treatments including dimethyl fumarate[21], natalizumab[22] and alemtuzumab[30]. Recently, alemtuzumab was shown to improve the EQ5D index and the EQ5D-VAS, and physical and mental health components of short form-36 questionaire[30]. It should be kept in mind, however, that pwRMS receiving alemtuzumab were unblinded to treatment allocation due to the infusions and infusion related reactions[31], which precludes accounting for placebo effects.

On the basis of the data collected during CLARITY[5,7], cladribine was highly effective in controlling MRI lesion accrual, relapses, and deterioration of disease-related disability[5,7], further corroborated by reduction in brain atrophy[32]. As a rule, high-efficacy DMT are currently associated with a higher frequency of treatment-related adverse effects, such as opportunistic infections, notably progressive multifocal leukoencephalopathy, and the development of secondary autoimmunities[33,34], which do not appear to be a feature of cladribine induction therapy[5,7,9]

Limitations

Reviewing the protocol and amendments of CLARITY between 2005 and 2008 suggests measuring QoL was not considered as important as in more recent trials. The EQ5D was the only index included in the first version (January 2005) of the CLARITY protocol, whilst MSQOL-54, 36-Item Short Form Survey (data not included due to small number of responses) and an analysis plan were only added later in 2005 and 2006. As a result, the EQ5D remained the only index for which the number of responses enabled robust analysis. Whilst the number of MSQOL-54 responses was limited, making it less straightforward to interpret how cladribine affected specific domains, the EQ5D dimension results indicate that cladribine broadly improved symptoms associated with self-care. The original analysis plan of CLARITY included comparative analysis between the two cladribine groups and the placebo group using Hochberg's step-up multiple comparison. However, we used ANCOVA methodology and planned contrast analysis, which are not significantly different.

In conclusion, we independently analysed QoL data collected during the largest ever trial of cladribine versus placebo in pwRMS. Over and above the established efficacy of cladribine on clinical outcomes[5,7], the treatment led to significant improvement in QoL. These results further underpin the potential of cladribine as a DMT for pwRMS, be it as a drug licensed for MS, as is currently being sought once again in Europe[35], or using an off-label preparation[6,12].

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Table 1: Mean change in EQ5D dimensions for cladribine and placebo groups

Treatment	Mobility	Self-Care	Activity	Pain	Anxiety
Placebo	0.04± 0.46	0.15 ± 0.50	0.03 ± 0.60	0.00 ± 0.59	0.08 ± 0.66
3.5mg/kg cladribine	-0.05 ± 0.41 N.S. P=0.013	0.05 ± 0.43 P=0.008	-0.02 ± 0.53 N.S. P>0.05.	-0.05 ± 0.59 N.S. P>0.05.	-0.03 ± 0.59 N.S. P=0.028
5.25mg/kg cladribine	-0.02 ± 0.45 N.S. P>0.05	0.05 ± 0.45 P=0.003	0.04 ± 0.60 N.S.P>0.05.	0.00 ± 0.62 N.S. P>0.05.	-0.02 ± 0.62 N.S. P=0.029

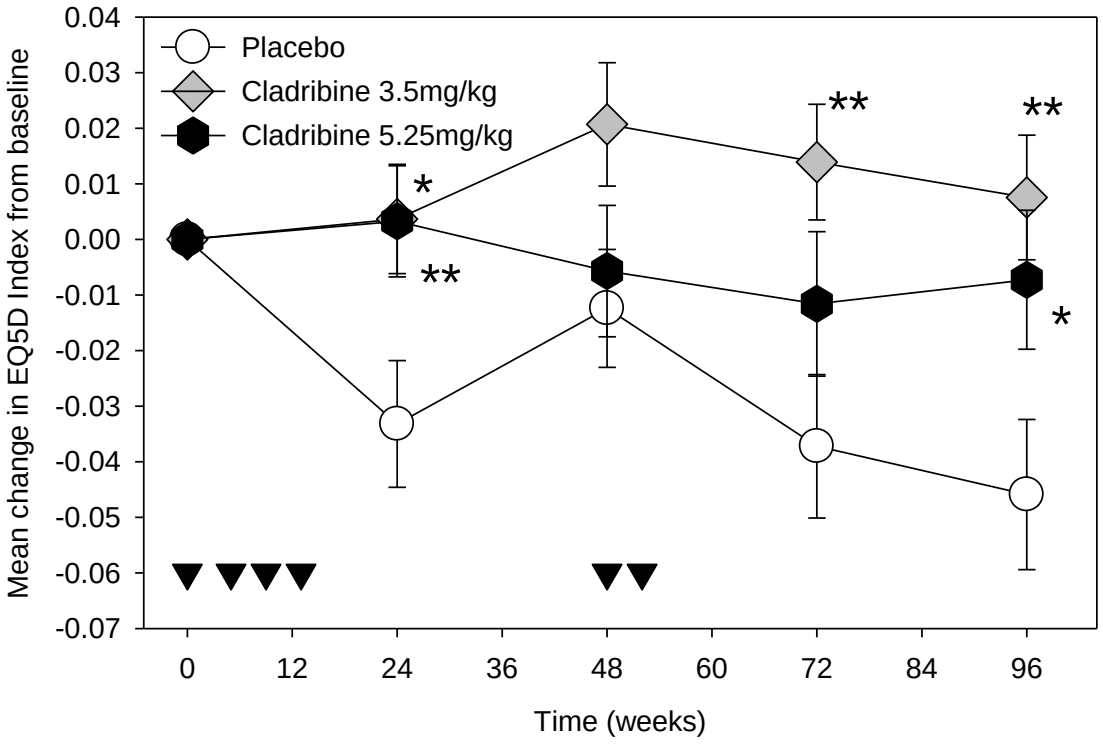
EQ5D was established at baseline and 96 weeks following treatment with either 3.5mg/kg or 5.25mg/kg. The results represent the mean ± standard deviation. Differences between treatment and placebo was assessed using ANCOVA. P<0.01 was considered significant for multiple comparisons involving 5 outcomes.

Table 2: Counts and proportions of participants achieving MCID for each treatment arm

Timepoint	Group	Number within MCID ≥ 0.08 (%)
Week 24	Cladribine 3.5	77 (36.8)
	Cladribine 5.25	70 (33.5)
	Placebo	62 (29.7)
Week 48	Cladribine 3.5	98 (39.5)
	Cladribine 5.25	77 (31.0)
	Placebo	73 (29.4)
Week 72	Cladribine 3.5	75 (33.6)
	Cladribine 5.25	82 (36.8)
	Placebo	66 (29.6)
Week 96	Cladribine 3.5	84 (35.7)
	Cladribine 5.25	87 (37.0)
	Placebo	64 (27.2)

Figure 1 The impact of cladribine on EQ5D

People with relapsing MS were treated with either placebo (circle; n= 281-310) or 3.5mg/kg cladribine (diamond; n= 306-319) on weeks 0, 5, 48 and 52 or treated with 5.25mg/kg (hexagon; n= 320-329) by receiving additional oral doses in weeks 9 and 13. The results represent the mean ± standard error of the mean. *p<0.05, **p<0.01 compared to placebo. Inverse triangles indicate time points of drug administration.



SUPPLEMENTARY DATA

Table S1: Baseline EQ5D respondents at baseline and in response to treatment

Variable	Placebo	Cladribine 3.5mg/kg	Cladribine 5.25mg/kg
EQ5D respondents at Baseline			
Mean Age (Range) Year	39.1 ± 9.7 (18-62)	38.2 ± 10.2 (18-65)	39.8 ± 9.6 (18-65)
Female Responses* (%)	1092 (65.9)	1200 (67.2)	1189 (69.8)
Median (Range) EDSS	3 (0-6)	3 (0-6)	3 (0-6)
EQ5D respondents at Baseline			
N (pwRMS)	349	353	370
Mean EQ5D Index (Range)	0.72 ± 0.19 (-0.04-1.00)	0.72 ± 0.20 (-0.02-1.00)	0.71 ± 0.21(-0.18-1.00)
Mean EQ5D VAS (Range)	68.9 ± 21.1 (0-100)	70.22 ± 19.1 (0-100)	69.1 ± 19.3 (0-100)
EQ5D respondents at 24 weeks			
N (pwRMS)	341	336	353
Mean EQ5D Index (Range)	0.68 ± 0.23 (-0.17-1.00)	0.72 ± 0.20 (-0.02-1.00)	0.71 ± 0.20(-0.08-1.00)
Mean EQ5D VAS (Range)	66.8 ± 21.7 (0-100)	70.7 ± 22.2 (18-100)	69.3 ± 19.1 (0-100)
EQ5D respondents at 48 weeks			
N (pwRMS)	318	338	354
Mean EQ5D Index (Range)	0.70 ± 0.22 (-0.24-1.00)	0.72 ± 0.22 (-0.18-1.00)	0.70 ± 0.23 (-0.18-1.00)
Mean EQ5D VAS (Range)	67.7 ± 20.6 (0-100)	70.7 ± 18.1 (0-100)	68.0 ± 21.3 (0-100)
EQ5D respondents at 72 weeks			
N (pwRMS)	312	332	350
Mean EQ5D Index (Range)	0.67 ± 0.26 (-0.43-1.00)	0.74 ± 0.20 (-0.18-1.00)	0.69 ± 0.25 (-0.26-1.00)
Mean EQ5D VAS (Range)	66.8 ± 21.2 (0-100)	71.5 ± 17.9 (0-100)	68.3 ± 20.8 (0-100)
EQ5D respondents at 96 weeks			
N (pwRMS)	338	345	359
Mean EQ5D Index (Range)	0.66 ± 0.26 (-0.33-1.00)	0.73 ± 0.22 (-0.02-1.00)	0.70 ± 0.23 (-0.17-1.00)
Mean EQ5D VAS (Range)	66.3 ± 22.6 (0-100)	71.9 ± 19.4 (0-100)	68.3 ± 20.7 (0-100)

Demographics and clinical characteristics of baseline EQ5D respondents in placebo, low dose and high dose cladribine groups. *Number of responses from all time points. Results represent mean ± standard deviation.

Table S2: Baseline MSQOL-54 respondents at baseline and in response to treatment

Variable	Placebo	Cladribine 3.5mg/kg	Cladribine 5.25mg/kg
MSQOL-54 respondents at Baseline			
Mean Age (Range) Year	38.3 ± 8.9 (19-58)	38.9 ± 10.1 (24-65)	42.0 ± 9.6 (19-65)
Female Responses* (%)	196 (68.5%)	204 (73.6%)	259 (78.2%)
Median (Range) EDSS	2.5 (0-5)	2.5 (1-6)	2.5 (1-6)
MSQOL-54 respondents at Baseline			
N (pwMS)	51	50	57
Mean PHS (Range) 0 week	54.0 ± 18.0 (16-92)	51.4 ± 17.1 (19-90)	54.5 ± 16.8 (24-85)
Mean MHS (Range) 0 week	70.0 ± 19.0 (23-96)	65.6 ± 19.3 (23-93)	69.4 ± 22.4 (12-97)
MSQOL-54 respondents at 24 weeks			
N (pwRMS)	55	45	63
Mean PHS (Range)	55.2 ± 16.7 (17-90)	52.6 ± 17.0 (35-92)	56.4 ± 18.9 (8-89)
Mean MHS (Range)	71.0 ± 18.4 (18-98)	69.2 ± 18.3 (33-92)	71.0 ± 22.4 (7-97)
MSQOL-54 respondents at 48 weeks			
N (pwRMS)	65	65	72
Mean PHS (Range)	52.2 ± 17.2 (17-91)	56.1 ± 21.8 (12-95)	54.2 ± 18.4 (13-96)
Mean MHS (Range)	71.0 ± 18.4 (18-98)	70.5 ± 20.5 (25-96)	68.8 ± 23.1 (11-97)
MSQOL-54 respondents at 72weeks			
N (pwRMS)	55	57	65
Mean PHS (Range)	54.6 ± 18.7 (20-91)	53.0 ± 20.6 (18-91)	52.7 ± 19.5 (10-89)
Mean MHS (Range)	68.3 ± 23.2 (11-97)	66.7 ± 20.5 (29-95)	68.8 ± 23.4 (10-96)
MSQOL-54 respondents at 96weeks			
N (pwRMS)	65	65	72
Mean PHS (Range)	52.2 ± 17.2 (17-91)	56.0 ± 20.7 (18-94)	56.7 ± 19.1 (12-90)
Mean MHS (Range)	68.5 ± 20.9 (14-99)	71.0 ± 21.1 (21-96)	71.4 ± 21.1 (24-95)

Demographics and clinical characteristics of baseline MSQOL-54 respondents in placebo, low dose and high dose cladribine groups. *Number of responses from all time points. Results represent mean ± standard deviation.