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Original Research Paper

Long-term follow-up of patients with relapsing multiple sclerosis from the CLARITY/ CLARITY Extension cohort of CLASSIC-MS: An ambispective study

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Abstract

Background: CLASSIC-MS evaluated the long-term efficacy of cladribine tablets in patients with relapsing multiple sclerosis.

Objective: Report long-term mobility and disability beyond treatment courses received in CLARITY/ CLARITY Extension.

Methods: This analysis represents CLASSIC-MS patients who participated in CLARITY with/without participation in CLARITY Extension, and received ⩾1 course of cladribine tablets or placebo ($N=435$). Primary objective includes evaluation of long-term mobility (no wheelchair use in the 3 months prior to first visit in CLASSIC-MS and not bedridden at any time since last parent study dose (LPSD), i.e. Expanded Disability Status Scale (EDSS) score <7). Secondary objective includes long-term disability status (no use of an ambulatory device (EDSS < 6) at any time since LPSD).

Results: At CLASSIC-MS baseline, mean ± standard deviation EDSS score was 3.9 ± 2.1 and the median time since LPSD was 10.9 (range = 9.3–14.9) years. Cladribine tablets–exposed population: 90.6% ($N=394$), including 160 patients who received a cumulative dose of 3.5 mg/kg over 2 years. Patients not using a wheelchair and not bedridden: exposed, 90.0%; unexposed, 77.8%. Patients with no use of an ambulatory device: exposed, 81.2%; unexposed, 75.6%.

Conclusion: With a median 10.9 years' follow-up after CLARITY/CLARITY Extension, findings suggest the sustained long-term mobility and disability benefits of cladribine tablets.

Keywords: Cladribine tablets, CLARITY, CLARITY Extension, disability, disease-modifying therapy, employment, Expanded Disability Status Scale, multiple sclerosis

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Introduction

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating, and neurodegenerative disease of the central nervous system that is most commonly diagnosed in young adults between the ages of 20 and 50 years,[1–3] and is typically characterized by frequent relapses paralleled by disability progression and cognitive impairment.[4]

Cladribine tablets (3.5 mg/kg cumulative dose over 2 years) is a high-efficacy disease-modifying therapy (DMT) approved for use in the treatment of relapsing MS, having shown significant benefits in both treatment naïve and treatment-experienced patients.[5–7] This agent has novel posology among available DMTs, in that it comprises a short treatment course at the beginning of the first and second months of two consecutive treatment years; thereafter, no further treatment with cladribine tablets is required in years 3 and 4, in view of sustained efficacy.

The CLARITY (**CLA**d**RI**bine **T**ablets for treating MS orall**Y**) study, which recruited patients between April 2005 and January 2007, was conducted at a time when limited high-efficacy treatments were available and the diagnosis of MS was based on the older 2001

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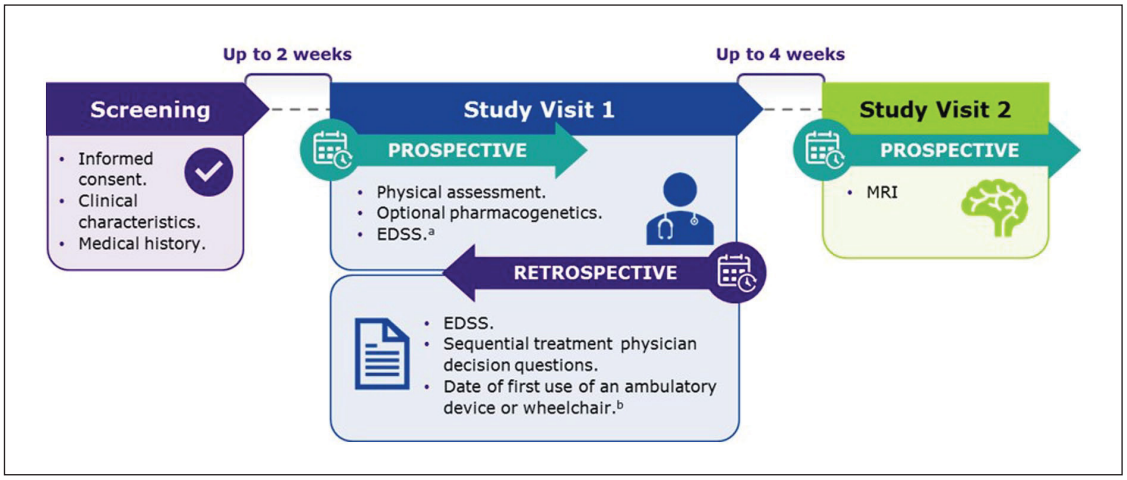

Figure 1. CLASSIC-MS study design.
EDSS: Expanded Disability Status Scale; MRI: magnetic resonance imaging.
[a]Can also be administered by telephone instead of in-person at clinic at Study Visit 1.
[b]May be determined through retrospective chart review and/or at Study Visit 1, for example, if conversion or disability progression occurred between last regular clinical visit and Study Visit 1.

McDonald criteria. Despite this, the results from CLARITY showed that short-course treatment with cladribine tablets significantly reduced relapse rates, the risk of disability progression, and improved magnetic resonance imaging (MRI) outcomes.[5] In turn, CLARITY Extension provided further evidence of the sustained efficacy of cladribine tablets.[6] Subsequent analysis of CLARITY Extension has indicated the sustained benefits of cladribine tablets in terms of no evidence of disease activity (NEDA-3), and for up to 6 years from the baseline of CLARITY.[8]

The CLASSIC-MS study (NCT03961204) was designed to further explore the long-term efficacy and durability of the effect of cladribine tablets beyond the two annual treatment courses in patients enrolled in the parent trials of the Phase III development program (CLARITY, CLARITY Extension, and ORACLE MS [**ORA**l **CL**adribine in **E**arly **M**ultiple **S**clerosis]). The analysis presented here focuses on the CLASSIC-MS patient population previously enrolled in CLARITY with or without subsequent enrollment to CLARITY Extension. Findings for the ORACLE MS cohort are to be reported elsewhere.

Methods

Study design and endpoints

CLASSIC-MS was an exploratory, low-interventional, multicenter, ambispective, Phase IV study of patients with MS (Figure 1), in which the assessment of patients took place across 98 centers in 29 countries between 2019 and 2021.

The analysis presented here concerns data for patients who participated in CLARITY with or without subsequent enrollment to CLARITY Extension, for which the median time to follow-up in CLASSIC-MS since the last parent study dose (LPSD) was 10.9 (range = 9.3–14.9) years. The time since LPSD was defined as the time since the last treatment dose of cladribine tablets or placebo during the parent study; this timing varies between patients depending on their enrollment in the CLARITY Extension study and the number of treatment courses received during CLARITY/CLARITY Extension (Supplemental Figure 1). To be eligible for inclusion in the current analysis, patients must have received ⩾1 course of cladribine tablets or placebo during the parent studies and must have been able to provide informed consent at the time of enrollment.

During the first study visit of CLASSIC-MS (hereafter referred to as "Study Visit 1"), retrospective data on Expanded Disability Status Scale (EDSS) score,[9] use of ambulatory device(s), relapses, and subsequent use of DMTs were collected along with employment status. For the purposes of analysis, "actively employed" included people who were "employed for wages," "self-employed," or considered themselves a "homemaker" at the time of Study Visit 1.

The primary objective of CLASSIC-MS was to evaluate long-term mobility by determining the proportion of patients not using a wheelchair in the 3 months prior to Study Visit 1 and not bedridden at any time since LPSD, as determined by a level of functioning consistent with an EDSS score <7. Where EDSS

scores were not available, alternative clinical descriptions in the medical records were used.

Secondary objectives were to assess long-term disability status by determining the proportion of patients not using an ambulatory device since LPSD. This was determined by a level of functioning consistent with an EDSS score <6 or alternative clinical descriptions.

The tertiary objectives were to determine real-world treatment patterns by assessing the number, type, and timing of subsequent DMT use, and the durability of clinical outcomes as assessed by the time from first [F]/[L]PSD to use of an ambulatory device.

In this study, a positive treatment response during the 4-year period since LPSD was defined using three variables, with responses categorized as "Yes," "No," and "Not determined":

(a) Not using further DMT(s);
(b) No evidence of disease reactivation based on medical records and investigator assessments of clinical outcomes; and
(c) Not using further DMT(s) and no evidence of disease reactivation.

Safety data were not evaluated as part of the CLASSIC-MS study, having been reported on as part of the parent studies.

Statistical analysis

Data evaluation and interpretation are based on point estimates and 95% confidence intervals (CIs). Due to the exploratory and hypothesis-generating nature of the study, no testing of formal statistical hypotheses or adjustments for multiple comparisons was performed. Time-to-event analyses are presented using the Kaplan–Meier estimates and cumulative incidence curves. Findings are presented according to patient exposure/non-exposure to cladribine tablets in the parent studies (i.e. CLARITY/CLARITY Extension), and separately for those who received a cladribine tablets dose of 3.5 mg/kg over 2 years. Analyses were performed using SAS® software version 9.4 or higher.

Results

A total of 435 patients from CLARITY with or without subsequent enrollment to CLARITY Extension (of whom 345 patients participated in both studies) were included in this analysis of CLASSIC-MS. This population had a median age of 52.5 (range = 32–79) years and was predominantly female (67.8%). Concerning disability, patients had a median EDSS score of 3.5 (range = 0.0–9.0) at Study Visit 1 of CLASSIC-MS compared with 2.5 (range = 0.0–5.5) at the parent study baseline. For patients exposed to cladribine tablets, there was a 1.0-point increase in median EDSS scores between the parent study baseline and Study Visit 1 compared with a 1.5-point increase in patients who were never exposed to active treatment. Of the 435 patients included in this analysis, 90.6% (394/435) had been exposed to cladribine tablets in the parent studies, with 160 patients having received a cumulative dose of 3.5 mg/kg over 2 years, with the other 234 patients having been exposed to varying doses of cladribine tablets during the parent studies (Supplemental Figure 1). Baseline characteristics of the exposed and never-exposed cohorts of CLASSIC-MS patients from CLARITY/CLARITY Extension were largely similar, as shown in Table 1. Overall, baseline disease characteristics of patients enrolled on CLASSIC-MS were similar to those who were not enrolled on the study (Supplemental Table 1).

Primary endpoint (median 10.9 years since LPSD)

In this study population, 88.9% of evaluable patients (369/415) were not using a wheelchair in the 3 months prior to Study Visit 1 and were not bedridden at any time since LPSD (i.e. EDSS < 7). This represented 77.8% (28/36) of patients who were never exposed to active treatment, compared with 90.0% (341/379) of patients who were exposed to cladribine tablets (odds ratio = 0.39, 95% CI = 0.17–0.93; $p = 0.034$) (Figure 2). For patients receiving cladribine tablets 3.5 mg/kg over 2 years, 88.2% (134/152) were not using a wheelchair and were not bedridden during these same time periods. When compared with the never-exposed cohort (36/41), this provided an odds ratio of 0.52 (95% CI = 0.20–1.33; $p = 0.173$).

In terms of time to the first use of an ambulatory device since LPSD (tertiary endpoint), 28.9% (114/394) of patients exposed to cladribine tablets and 46.3% (19/41) of never-exposed patients had an event with an estimated time of 9.9 and 7.2 years for 25% of patients to reach an event, respectively (Figure 3).

Secondary endpoint (median 10.9 years since LPSD)

In this study population, 80.7% (351/435) of patients did not use an ambulatory device at any time since

Table 1. Patient demographics and disease characteristics at parent study baseline and Study Visit 1 of CLASSIC-MS: CLARITY/CLARITY Extension cohort.

Parameter	Never exposed to cladribine tablets[a] (*N*=41)	Exposed to cladribine tablets		Total (*N*=435)
		All exposed patients[b] (*N*=394)	Subgroup exposed to 3.5 mg/kg dose[c] (*N*=160)	
Female, *n* (%)	31 (75.6)	264 (67.0)	103 (64.4)	295 (67.8)
Age at Study Visit 1 (years), mean ± SD	51.6 ± 10.25	52.8 ± 9.56	51.7 (9.76)	52.7 ± 9.62
Disease duration at Study Visit 1[d] (years), mean ± SD	22.38 ± 6.85	22.36 ± 6.99	21.32 ± 6.21	22.36 ± 6.97
Time since the last dose in the parent study to Study Visit 1 (years)				
Mean ± SD	13.50 ± 0.47	11.14 ± 1.17	11.05 ± 1.15	11.35 ± 1.31
Median (range)	13.40 (12.4–14.5)	10.79 (9.3–14.9)	10.65 (9.5–14.4)	10.89 (9.3–14.9)
Duration of treatment during parent study (years)[e]				
Mean ± SD	0.85 ± 0.31	1.86 ± 1.27	1.01 ± 0.05	1.77 ± 1.25
Median (range)	0.99 (0.1–1.2)	1.01 (0.0–4.6)	0.99 (0.9–1.2)	1.00 (0.0–4.6)
EDSS score at parent study baseline				
Mean ± SD	2.74 ± 1.33	2.82 ± 1.29	2.74 ± 1.31	2.82 ± 1.29
Median (range)	3.00 (0.0–5.5)	2.50 (0.0–5.5)	2.50 (0.0–5.5)	2.50 (0.0–5.5)
EDSS score at Study Visit 1				
Mean ± SD	4.50 ± 2.59	3.82 ± 2.01	3.78 ± 2.07	3.87 ± 2.07
Median (range)	4.50 (0.0–9.0)	3.50 (0.0–9.0)	3.50 (0.0–9.0)	3.50 (0.0–9.0)
Number of relapses in the 12 months before enrollment to parent study, mean ± SD	1.6 ± 0.78	1.3 ± 0.59	1.3 ± 0.62	1.3 ± 0.62
Type of MS at CLASSIC-MS screening, *n* (%)				
RRMS	29 (70.7)	292 (74.1)	116 (72.5)	321 (73.8)
SPMS	12 (29.3)	102 (25.9)	44 (27.5)	114 (26.2)
Prior use of DMT at parent study baseline, *n* (%)	11 (26.8)	83 (21.1)	34 (21.3)	94 (21.6)
HDA[f] status at parent study baseline, *n* (%)	18 (43.9)	110 (27.9)	48 (30.0)	128 (29.4)
Employment status at Study Visit 1, *n* (%)				
Employed for wages	8 (19.5)	146 (37.1)	60 (37.5)	154 (35.4)
Self-employed	0 (0)	23 (5.8)	10 (6.3)	23 (5.3)
Homemaker	3 (7.3)	32 (8.1)	16 (10.0)	35 (8.0)
Retired	7 (17.1)	74 (18.8)	26 (16.3)	81 (18.6)
Out of work/unable to work	14 (34.1)	82 (20.8)	34 (21.3)	96 (22.1)
Unknown[g]	9 (22.0)	37 (9.4)	14 (8.8)	46 (10.6)

DMT: disease-modifying therapy; EDSS: Expanded Disability Status Scale; FPSD: first parent study dose; HDA: high disease activity; LPSD: last parent study dose; MS: multiple sclerosis; RRMS: relapsing-remitting multiple sclerosis; SD: standard deviation; SPMS: secondary progressive multiple sclerosis.
[a]Never-exposed cohort received only placebo during the parent studies.
[b]Exposed cohort includes all patients who received ⩾1 dose of cladribine tablets during the parent studies.
[c]A subgroup of the exposed cohort in which patients received 3.5 mg/kg cumulative dose over 2 years during the parent studies (*N*=160/394).
[d]Disease duration=(Study Visit 1−date of MS diagnosis + 1)/365.25.
[e]Treatment duration=(LPSD−FPSD + 1)/365.25.
[f]Defined as patients with ⩾2 relapses in the 12 months prior to parent study entry, regardless of prior DMT use, OR patients with ⩾1 relapse in the previous 12 months and ⩾1 T1 gadolinium-enhancing lesion or ⩾9 T2 lesions while on therapy with other DMTs.
[g]Includes those with missing/not reported data or information not collected at study site.

LPSD (i.e. EDSS < 6). For patients who were never exposed to active treatment, the corresponding proportion was 75.6% (31/41) compared with 81.2% (320/394) of patients who were exposed to cladribine tablets (Figure 4). For patients receiving cladribine tablets 3.5 mg/kg over 2 years, 78.8% (126/160) did not use an ambulatory device at any time since LPSD.

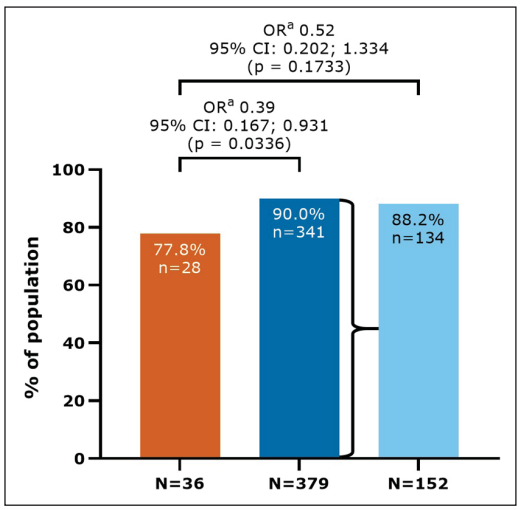

Figure 2. Patients not using a wheelchair in the 3 months prior to Study Visit 1 and not bedridden at any time since LPSD (EDSS < 7): CLARITY/CLARITY Extension cohort.
CI: confidence interval; EDSS: Expanded Disability Status Scale; LPSD: last parent study dose; OR: odds ratio.
Missing data were not included in the analysis ($n=5$, $n=15$, and $n=8$ for never exposed, exposed, and exposed to cladribine tablets 3.5 mg/kg over 2 years, respectively).
[a]From a logistic regression model with fixed effects for treatment group and disease duration.
[b]Never-exposed cohort received only placebo during the parent studies.
[c]Exposed cohort includes all patients who received ⩾1 dose of cladribine tablets during the parent studies.
[d]A subgroup of the exposed cohort in which patients received 3.5 mg/kg cumulative dose over 2 years during the parent studies ($N=160/394$).

Response at 4 years since LPSD

Findings of the 4-year responder analyses indicated that 63.4% (276/435) of patients did not use a subsequent DMT; 48.0% (209/435) showed no evidence of disease reactivation, and 32.6% (142/435) did not use a subsequent DMT and also showed no evidence of disease reactivation (Table 2).

When analyzed by cohort, 66.2% (261/394) of patients exposed to cladribine tablets used no subsequent DMT(s) compared with 36.6% (15/41) in the never-exposed cohort. No evidence of disease reactivation was observed in 50.3% (198/394) of patients exposed to cladribine tablets compared with 26.8% (11/41) in the never-exposed cohort. For patients not using a subsequent DMT *and* showing NEDA, 34.5% (136/394) of patients exposed to cladribine tablets met these criteria compared with 14.6% (6/41) of patients in the never-exposed cohort. For patients receiving cladribine tablets 3.5 mg/kg over 2 years, results for the 4-year responder analyses were comparable to the exposed cohort. Results also indicate that patients with high relapse activity responded well to treatment with cladribine tablets (Supplemental Table 2).

Subsequent DMT use (median 10.9 years since LPSD)

Over the period since LPSD, 53.1% (231/435) of patients did not use any subsequent DMTs. The majority of patients who used a subsequent treatment received a platform injectable (137/204, 67.2%), namely, interferons (94/137, 68.6%) (Supplemental Table 3). These subsequent DMTs are reflective of those available in the intervening period (2010–2021) after the completion of the parent studies.

Patients exposed to cladribine tablets during the parent studies were less likely to use further DMTs after LPSD. This is indicated by 55.8% (220/394) of the exposed cohort, versus 26.8% (11/41) in the never-exposed cohort, receiving no subsequent treatments during follow-up (Figure 5). For patients receiving cladribine tablets 3.5 mg/kg over 2 years, 58.1% (93/160) received no further DMTs after LPSD.

In terms of time-to-event analysis, patients exposed to cladribine tablets had an estimated median time of 12.0 years until the first subsequent DMT; the corresponding timeframe for patients never exposed to cladribine tablets was 2.8 years (Figure 6). The corresponding time-to-event analysis for the subgroup receiving 3.5 mg/kg indicates that the data are similar to those for the exposed cohort (Figure 6).

A low proportion of patients received a second subsequent DMT following treatment with cladribine tablets; 14.2% (56/394) of patients exposed to cladribine tablets and 29.2% (12/41) of never-exposed patients. For patients receiving cladribine tablets 3.5 mg/kg over 2 years, 18.8% (30/160) received a second subsequent DMT.

The proportions of patients receiving a third subsequent DMT were lower still; 7.3% (3/41) never exposed, 4.6% (18/394) exposed to cladribine tablets, and 6.9% (11/160) of those who received the 3.5 mg/kg dose over 2 years.

Relapses (median 10.9 years since LPSD)

During the time period since LPSD to Study Visit 1, a total of 200 patients did not experience a relapse. The proportion of patients in the exposed cohort who were relapse-free was approximately two times higher than

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