

Efficacy of Cladribine Tablets in high disease activity subgroups of patients with relapsing multiple sclerosis: A post hoc analysis of the CLARITY study

Gavin Giovannoni, Per Soelberg Sorensen, Stuart Cook, Kottil W Rammohan, Peter Rieckmann, Giancarlo Comi, Fernando Dangond, Christine Hicking and Patrick Vermersch

Abstract

Background: In the CLARITY (CLADribine Tablets treating multiple sclerosis orally) study, Cladribine Tablets significantly improved clinical and magnetic resonance imaging (MRI) outcomes (vs placebo) in patients with relapsing-remitting multiple sclerosis.

Objective: Describe two clinically relevant definitions for patients with high disease activity (HDA) at baseline of the CLARITY study (utility verified in patients receiving placebo) and assess the treatment effects of Cladribine Tablets 3.5 mg/kg compared with the overall study population.

Methods: Outcomes of patients randomised to Cladribine Tablets 3.5 mg/kg or placebo were analysed for subgroups using HDA definitions based on high relapse activity (HRA; patients with ≥ 2 relapses during the year prior to study entry, whether on DMD treatment or not) or HRA plus disease activity on treatment (HRA + DAT; patients with ≥ 2 relapses during the year prior to study entry, whether on DMD treatment or not, PLUS patients with ≥ 1 relapse during the year prior to study entry while on therapy with other DMDs and ≥ 1 T1 Gd+ or ≥ 9 T2 lesions).

Results: In the overall population, Cladribine Tablets 3.5 mg/kg reduced the risk of 6-month-confirmed Expanded Disability Status Scale (EDSS) worsening by 47% vs placebo. A risk reduction of 82% vs placebo was seen in both the HRA and HRA + DAT subgroups (vs 19% for non-HRA and 18% for non-HRA + DAT), indicating greater responsiveness to Cladribine Tablets 3.5 mg/kg in patients with HDA. There were consistent results for other efficacy endpoints. The safety profile in HDA patients was consistent with the overall CLARITY population.

Conclusion: Patients with HDA showed clinical and MRI responses to Cladribine Tablets 3.5 mg/kg that were generally better than, or at least comparable with, the outcomes seen in the overall CLARITY population.

Keywords: Cladribine Tablets, high disease activity, efficacy, safety, risk:benefit

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Introduction

There is considerable variability among patients with multiple sclerosis (MS), particularly in their response to therapy with disease-modifying drugs (DMDs).^{1–3} Poorer prognosis for patients with MS can be predicted by relapses and magnetic resonance imaging (MRI) disease activity during treatment.^{4,5} The combination of clinical and MRI parameters has also been used to monitor the response of patients to therapy and predict the likelihood of future clinical events and

worsening of disability.^{6–9} Assessing the benefit:risk balance is key to selecting the appropriate treatment for patients, with respect to the risk of future relapses or disability worsening.¹⁰

Efficacy of Cladribine Tablets (MAVENCLAD®; Merck Serono Europe Ltd, London, UK), in patients with relapsing MS, has been demonstrated in the CLARITY study on the basis of clinical and MRI

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Correspondence to:

G Giovannoni
Department of Neurology,
Blizard Institute, Barts
and The London School of
Medicine and Dentistry,
Queen Mary University of
London, 4 Newark Street,
London E1 2AT, UK.
g.giovannoni@qmul.ac.uk

Gavin Giovannoni
Department of Neurology,
Blizard Institute, Barts
and The London School of
Medicine and Dentistry,
Queen Mary University of
London, London, UK

Per Soelberg Sorensen
Danish Multiple Sclerosis
Center, Department of
Neurology, Rigshospitalet,
University of Copenhagen,
Copenhagen, Denmark

Stuart Cook
Department of Neurology &
Neurosciences, New Jersey
Medical School, Rutgers,
The State University of New
Jersey, Newark, NJ, USA

Kottil W Rammohan
MS Research Center,
Department of Neurology,
University of Miami Miller
School of Medicine, Miami,
FL, USA

Peter Rieckmann
Department of Neurology,
Hospital for Nervous
Diseases, Medical Park Loipl,
Bischofswiesen, Germany/
University of Erlangen-
Nürnberg, Erlangen,
Germany

Giancarlo Comi
Department of Neurology,
Università Vita-Salute San
Raffaele and Institute of
Experimental Neurology,
Ospedale San Raffaele,
Milan, Italy

Fernando Dangond
EMD Serono, Inc., Billerica,
MA, USA

Christine Hicking
Merck KGaA, Darmstadt,
Germany

Patrick Vermersch
University of Lille, CHU
Lille, LIRIC-INSERM U995,
FHU Imminent, Lille, France

measurements, or the composite endpoint of no evidence of disease activity (NEDA).^{11,12} Furthermore, the CLARITY Extension study showed that treatment with Cladribine Tablets administered as two short (4 or 5 days) weekly treatments at the start of months 1 and 2 in each treatment year, followed by no additional active treatment produced durable clinical benefits.¹³ Patients with relapsing MS who show an increased rate of relapse or disability progression can be described as having high disease activity (HDA). The current manuscript describes definitions of HDA used in new post hoc analyses of the CLARITY study. In the summary of product characteristics (SmPC) of fingolimod and natalizumab, the European Medicines Agency (EMA) has previously defined patients with HDA as those with ‘rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium-enhancing (Gd+) lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI’. The application of such criteria often depends on the availability of repeated clinical or imaging observations, which may unnecessarily delay treatment in precisely the patients who most need appropriate therapy. Therefore, due to the heterogeneity of MS and lack of agreed definitions or consensus for identifying patients with HDA, the current analyses were conducted using retrospective information on relapses in the year before the CLARITY study began and a single baseline MRI scan. Consequently, two definitions of HDA were used: one is based on relapse rate, which can identify patients with higher clinical disease activity, and the other is based on a combination of relapse rate and poor response to treatment as assessed by MRI activity, which can identify patients with higher overall levels of disease activity.

Therefore, the objectives of this manuscript are to describe the two clinically relevant definitions of patients with HDA and to verify the utility of the definitions by presenting assessments of clinical activity from patients treated with placebo in the CLARITY study. The treatment effects of Cladribine Tablets 3.5 mg/kg in subgroups of patients, meeting or not meeting the definitions of HDA in the CLARITY study, are also described. Treatment outcomes for the subgroups were compared with those for the overall study population (comprising both HDA and non-HDA patients).

Methods

The methods and outcomes of the CLARITY study have been published previously.¹¹ Briefly, the study enrolled male and female patients aged 18–65 years with a definite diagnosis of relapsing-remitting multiple sclerosis (RRMS) according to the 2005

McDonald criteria,¹⁴ including at least one relapse in the last 12 months before study entry, but no relapses in the 28 days before entry, neurological lesions detectable by MRI consistent with MS, and an Expanded Disability Status Scale (EDSS) score of 0–5.5.

In CLARITY, patients were excluded if they had received immunosuppressive therapy at any time before study entry or cytokine-based therapy, intravenous immune globulin therapy, or plasmapheresis within 3 months before study entry, or if previous treatment with two or more DMDs had failed. Eligible patients were assigned (1:1:1) to either Cladribine Tablets 3.5 mg/kg, 5.25 mg/kg (cumulative dose over 96 weeks) or matching placebo.

Based on evidence that relapse activity and MRI lesions have an influence on disability worsening in clinical studies,^{4–9} the two HDA criteria developed were retrospectively applied in order to identify such patients and evaluate their response to Cladribine Tablets. Because of the better benefit:risk ratio seen with the lower dose in the CLARITY study, the current retrospective analysis presents data for patients randomised to Cladribine Tablets 3.5 mg/kg ($N=433$) or placebo ($N=437$) using the two different HDA definitions, based on relapse history, prior treatment and MRI characteristics.

Cladribine Tablets were granted marketing authorisation by the European Commission on 25 August 2017 for the treatment of highly active relapsing MS as defined by clinical or imaging features. The results presented in the manuscript correspond to definitions of HDA given in the EMA SmPC for the approved product that correspond to treatment-naïve patients with relapse activity or patients with evidence of disease activity while on treatment with a DMD.¹⁵

Subgroup analyses

Two overlapping sets of criteria were retrospectively applied in the analysis of baseline disease characteristics to subdivide patients into HDA groups (Figure 1). The first, which is referred to in this manuscript as the high relapse activity (HRA) subgroup, comprises patients with ≥ 2 relapses during the year prior to study entry, whether on DMD treatment or not. The second, which is referred to as the HRA plus disease activity on treatment (HRA+DAT) subgroup, comprises patients with ≥ 2 relapses during the year prior to study entry, whether on DMD treatment or not, and patients with ≥ 1 relapse and during the year prior to study entry while on therapy with other DMDs and ≥ 1 T1 Gd+ or ≥ 9 T2 lesions.

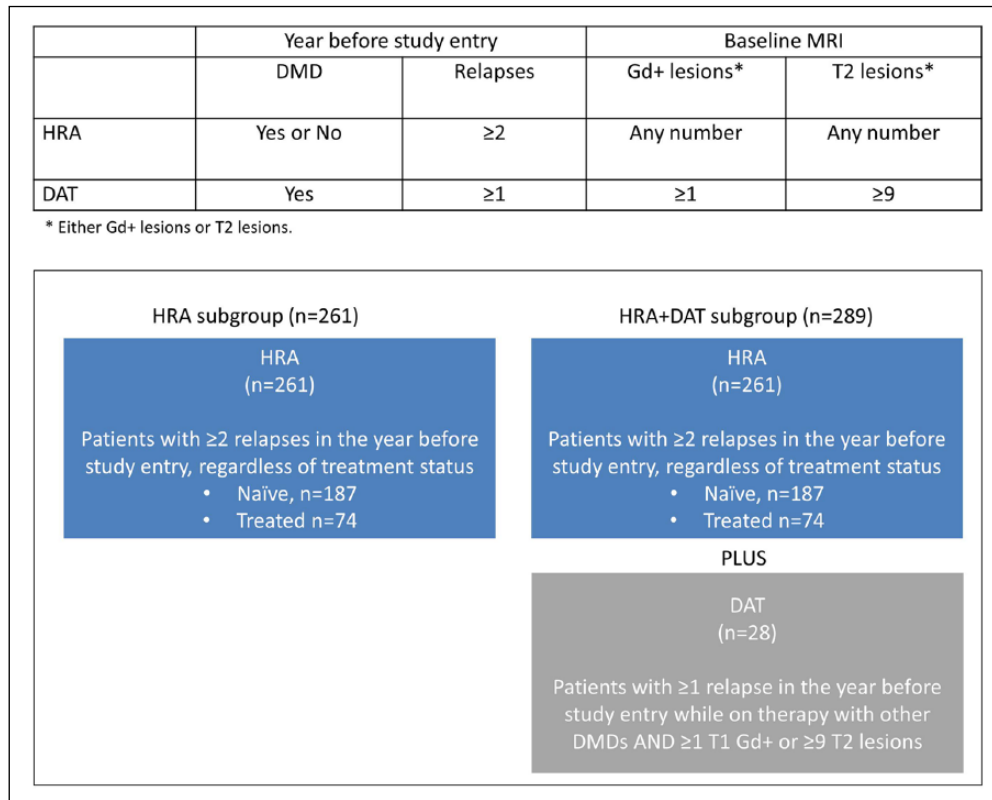


Figure 1. Definitions used for the HRA and HRA+DAT subgroups.

DMD: disease modifying drug; DAT: disease activity on treatment; HRA: high relapse activity; HRA+DAT: high relapse activity plus disease activity on treatment.

Disease activity determination in placebo-treated patients. The utility of these criteria to retrospectively identify patients with HDA among patients receiving placebo was assessed by examining annualised relapse rate (ARR), time to first qualifying relapse and time to 6-month-confirmed EDSS worsening in this arm of the study. If placebo-treated patients who fulfilled the criteria for either HDA definition departed from the clinical behaviour of the overall population (comprising both HDA and non-HDA patients) by manifesting evidence of higher disease activity during the first 2 years of the study, this was considered verification of the utility of the criteria used to define HDA.

Effect of treatment with Cladribine Tablets in subgroups of patients based on HDA definitions. Efficacy analyses from CLARITY assessed the overall population, the HRA and HRA+DAT subgroups and corresponding non-HRA and non-HRA+DAT subgroups, based on time to 6-month-confirmed EDSS worsening, ARR, time to first qualifying relapse and the proportion of patients achieving NEDA. Data on 3-month-confirmed EDSS worsening and MRI outcomes were also analysed. Safety data for applicable subgroups and comparisons with the overall population are included.

Statistics

All analyses were post hoc and not pre-specified; no multiplicity adjustments were done to the resulting *p*-values. All comparisons where the *p*-value was less than 0.05 by statistical testing should be regarded as nominally significant. The efficacy parameters were analysed by various models. Time to first qualifying relapse and time to EDSS worsening were analysed by Cox proportional hazards model, and Kaplan–Meier estimates are presented. Endpoints based on proportions of subjects (NEDA score) were analysed by a logistic regression model. Qualifying relapse rate was analysed by Poisson regression model with fixed effects for treatment and number of relapses in the previous year and the log of time on study as the offset variable. The cumulative number of lesions was analysed by a negative binomial regression model with fixed effects for treatment group and study, with baseline number of lesions as covariate and with the log of number of scans as the offset variable. Subgroup by treatment interaction was analysed by Cox proportional hazard model adjusted for treatment, subgroup, subgroup-by-treatment interaction and baseline values as covariates.

Note that the analyses presented for the overall CLARITY population are slightly different to those in

Table 1. Outcomes in patients treated with placebo in CLARITY (overall and in HRA and HRA+DAT subgroups).

	Overall N=437	HRA N=131	Non-HRA N=306	HRA+DAT N=149	Non-HRA+DAT N=288
ARR (95% CI)	0.35 (0.31–0.39)	0.50 (0.41–0.60)	0.29 (0.24–0.34)	0.47 (0.40–0.57)	0.29 (0.24–0.34)
Time to first qualifying relapse (20% patients), days (95% CI)	225 (153–280)	127 (84–236)	260 (174–407)	144 (90–237)	260 (156–433)
Time to 6-month-confirmed EDSS worsening (10% patients), days (95% CI)	245 (127–345)	110 (85–245)	330 (161–497)	162 (85–247)	329 (156–498)

ARR: annualised relapse rate; CI: confidence interval; EDSS: Expanded Disability Status Scale; HRA: high relapse activity; HRA+DAT: high relapse activity plus disease activity on treatment.
Percentiles are estimated from a Kaplan–Meier survival curve.

the original publication.¹¹ In the current report, data are derived from an integrated database which included other studies with Cladribine Tablets; imputation methods were aligned between studies resulting in these slight differences.

Results

Baseline demographics and disease characteristics for the intent-to-treat (ITT) population are shown in Supplementary Table 1 and for the safety population in Supplementary Table 2. Apart from characteristics used to define the subgroups (i.e. relapses in the 12 months before the study, prior use of DMDs and MRI activity), patient demographics and other disease characteristics at baseline were similar across the subgroups of patients who met or did not meet the HRA or HRA+DAT criteria and the overall population of patients. Patients in the HRA and HRA+DAT subgroups had shorter disease duration at study baseline than the non-HDA counterpart subgroups and the overall population.

The overall efficacy analysis based on the ITT population involved 870 patients randomised to placebo (N=437) or Cladribine Tablets 3.5 mg/kg (N=433). Of those who met the HRA criteria, 131 were randomised to placebo and 130 to Cladribine Tablets 3.5 mg/kg (Supplementary Table 1). Among the non-HRA patients, 306 were randomised to placebo and 303 to Cladribine Tablets 3.5 mg/kg. Of those who met the HRA+DAT criteria, 149 were randomised to placebo and 140 to Cladribine Tablets 3.5 mg/kg. Among the non-HRA+DAT patients, 288 were randomised to placebo and 293 to Cladribine Tablets 3.5 mg/kg.

Outcomes in subgroups of patients receiving placebo in CLARITY

ARR was higher in the placebo-treated HRA and HRA+DAT subgroups than in the overall placebo

population and the placebo-treated groups who did not meet these criteria (Table 1). Both time to first qualifying relapse and time to 6-month-confirmed EDSS worsening were shorter for placebo-treated patients in the HRA and HRA+DAT subgroups, than in the overall placebo population and the placebo-treated groups who did not meet these criteria (Table 1). The increased ARR and shorter times to relapse and EDSS worsening in these placebo-treated patients, highlight the increased rates of disease activity in patients retrospectively identified using the HRA and HRA+DAT criteria and verify the utility of these criteria for assessing the clinical efficacy of Cladribine Tablets 3.5 mg/kg in patients with HDA.

Outcomes in subgroups of patients receiving Cladribine Tablets 3.5 mg/kg in CLARITY

In the overall CLARITY population (N=870), Cladribine Tablets 3.5 mg/kg reduced the risk of 6-month-confirmed EDSS worsening by 47% (hazard ratio (HR)=0.53, 95% confidence interval (CI)=0.36–0.79; $p=0.0016$) vs placebo (Figure 2). A larger risk reduction in time to 6-month-confirmed EDSS worsening for Cladribine Tablets 3.5 mg/kg vs placebo of 82% was seen in HRA patients and in HRA+DAT patients. Interaction p -values indicated that this increase was significant (interaction p -values; $p=0.0036$ for HRA vs non-HRA, and $p=0.0037$ for HRA+DAT vs non-HRA+DAT).

The effects of Cladribine Tablets 3.5 mg/kg in patients meeting the criteria for HDA were also demonstrated for time to 3-month-confirmed EDSS worsening (72% risk reduction in both HDA subgroups vs 20% for both non-HDA subgroups; see Supplementary Figure 1 for details).

For ARR, the relative risk (RR) ratio favoured Cladribine Tablets 3.5 mg/kg in the overall population (RR=0.42, 95% CI=0.33–0.52; $p<0.0001$; Figure 3). The RR ratios also favoured Cladribine Tablets 3.5 mg/

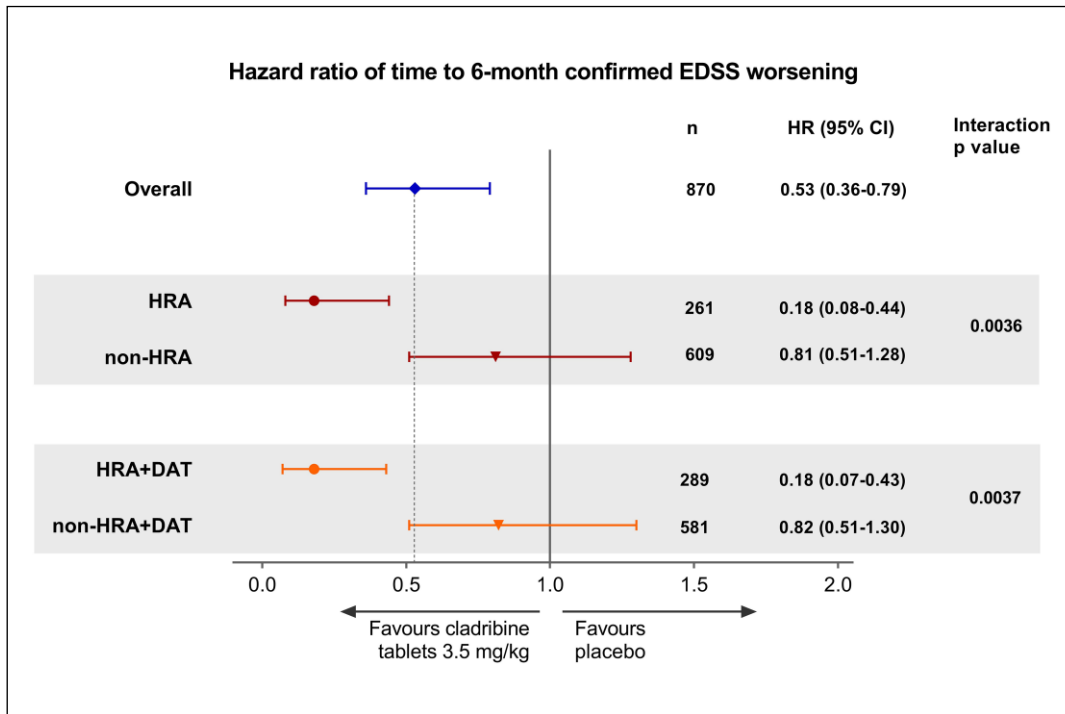


Figure 2. Forest plot of hazard ratio of time to 6-month-confirmed EDSS worsening by HDA subgroup for Cladribine Tablets 3.5 mg/kg vs placebo. EDSS: Expanded Disability Status Scale; HDA: high disease activity; HRA: high relapse activity; HRA+DAT: high relapse activity plus disease activity on treatment.

kg in each HDA subgroup and indicated even larger reductions in RR for patients who met the criteria for HRA and HRA+DAT compared with the overall population. However, the interaction *p*-values did not reach significance (Figure 3). Time to first qualifying relapse in the subgroups of patients meeting criteria for HDA at baseline are shown in Supplementary Figure 2.

The RR of cumulative new T1 Gd+ lesions for patients in both HDA subgroups treated with Cladribine Tablets 3.5 mg/kg was low, with strong effects observed in each treatment subgroup (Figure 4). Similar results were seen for analyses performed for active T2 lesions and combined unique lesions (see Supplementary Figures 3 and 4).

For assessment of disease-free status, NEDA was selected and defined as no relapses, no 3-month-confirmed EDSS worsening, no T1 Gd+ lesions and no active T2 lesions. Odds ratios (ORs) for the HRA and HRA+DAT subgroups were 8.02, 95% CI=3.93–16.35; $p < 0.0001$ and 7.82, 95% CI=4.03–15.19; $p < 0.0001$, respectively (Figure 5). Observed point estimates in HDA subgroups were systematically more favourable than the respective non-HDA subgroups, although not reaching significance except for HRA+DAT ($p = 0.0435$; Figure 5).

Safety

Overall, review of the safety data for the HRA and HRA+DAT subgroups did not reveal evidence for new safety findings compared with those described for the overall CLARITY population (Table 2).¹⁶ Baseline demographics and disease characteristics for the safety population are shown in Supplementary Table 2. It should be noted that the HRA and HRA+DAT subgroups included a lower number of patients than the corresponding non-HRA and non-HRA+DAT subgroups; therefore, comparisons need to be considered with caution.

Discussion

Disease activity, in both treated or treatment-naïve patients with relapsing MS, can be predictive of future disease worsening and overall poor prognosis.^{4,17–20} Consequently, it is important to study the effects of DMDs in patients with HDA who may be at risk for poor long-term clinical outcomes. Clinical and MRI markers of MS disease activity are of value in assessing the therapeutic effects of DMDs and have been used to predict patients at risk of disease worsening and disability worsening.^{4,17,18} Patients included in the CLARITY study had at least one relapse in the last 12 months before study entry, so had active disease, but the current analyses further explored the association of

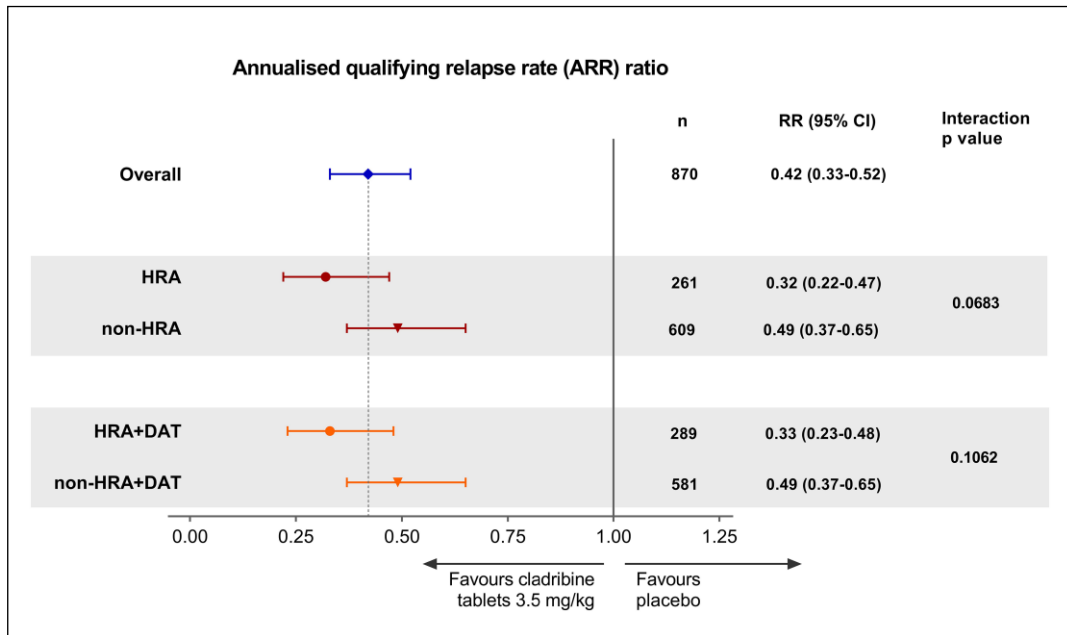


Figure 3. Forest plot of relative risk of ARR by HDA subgroup for Cladribine Tablets 3.5 mg/kg vs placebo. ARR: Annualised Relapse Rate; HDA: high disease activity; HRA: high relapse activity; HRA + DAT: high relapse activity plus disease activity on treatment.

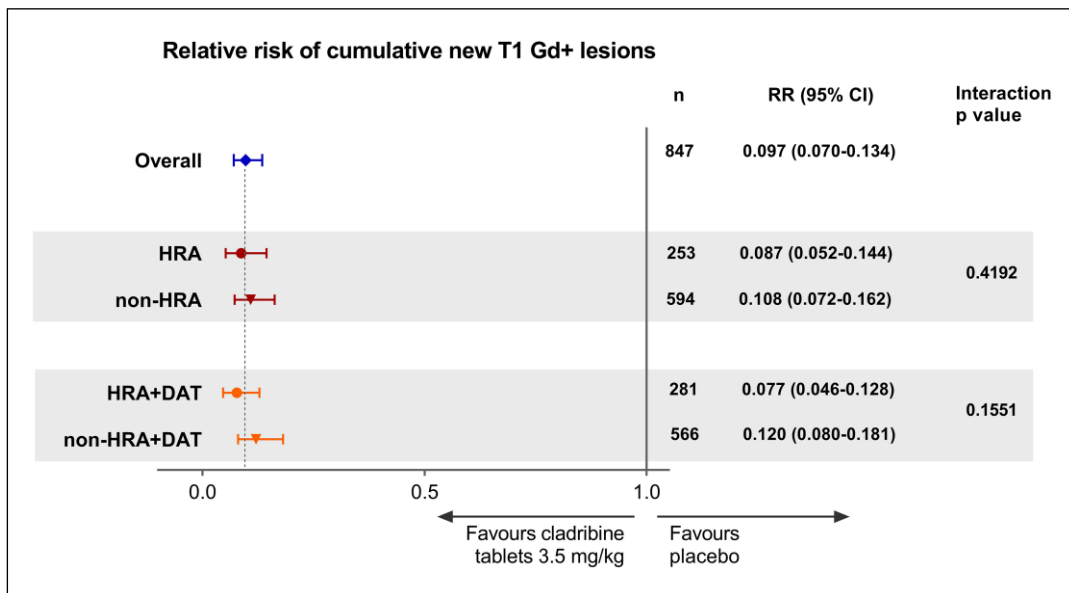


Figure 4. Forest plot of relative risk of cumulative number of new T1 Gd+ lesions by HDA subgroups for Cladribine Tablets 3.5 mg/kg vs placebo. Gd+, gadolinium enhancing; HDA: high disease activity; HRA: high relapse activity; HRA+DAT: high relapse activity plus disease activity on treatment.

baseline characteristics and treatment outcome.¹¹ The HDA subgroups presented in this analysis included patients with a wide variety of clinical histories, including both treatment-naïve and previously treated patients with relapsing MS.

Analysis of the placebo arm in the CLARITY study shows that the criteria for the HRA and HRA + DAT subgroups can identify patients who are more likely to experience both relapses and EDSS worsening. Specifically, patients meeting these criteria had

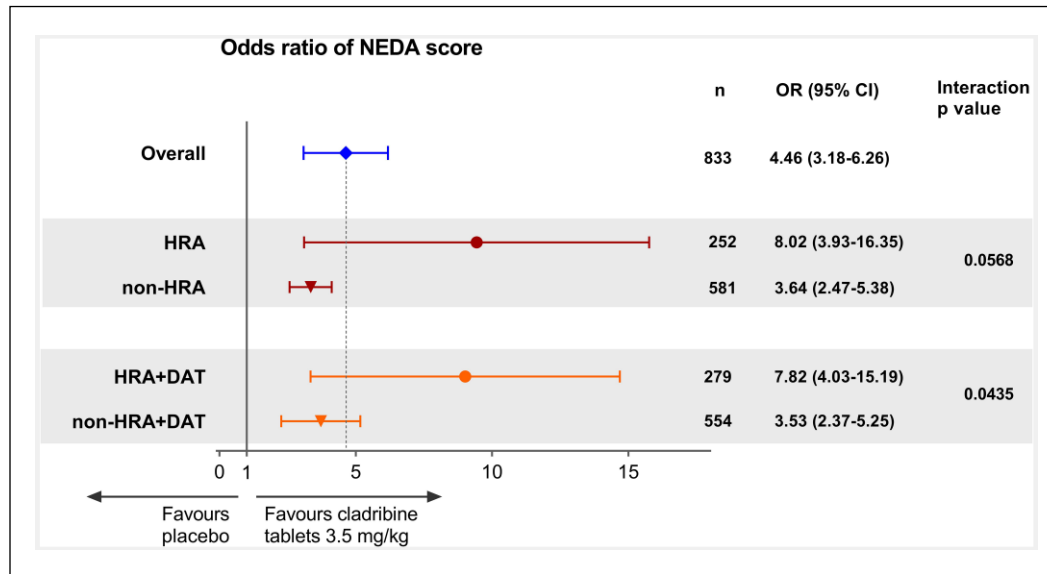


Figure 5. Forest plot of odds ratio of NEDA score by HDA subgroups for Cladribine Tablets 3.5 mg/kg vs placebo. Gd⁺; gadolinium enhancing; HDA: high disease activity; HRA: high relapse activity; HRA+DAT: high relapse activity plus disease activity on treatment; NEDA: no evidence of disease activity (defined as no relapses, no 3-month confirmed EDSS worsening, no T1 Gd⁺ lesions and no active T2 lesions).

Table 2. Summary of safety data for Cladribine Tablets 3.5 mg/kg by HDA subgroup (safety population).

Characteristic	Placebo			Cladribine Tablets 3.5 mg/kg		
	Overall N=433	HRA N=131	HRA+DAT N=148	Overall N=442	HRA N=131	HRA+DAT N=142
Any treatment-emergent AE, n (%)	317 (73.2)	100 (76.3)	112 (75.7)	359 (81.2)	99 (75.6)	109 (76.8)
95% CI	68.8–77.3	68.1–83.3	67.9–82.3	77.3–84.8	67.3–82.7	68.9–83.4
Any treatment-related AE, n (%)	167 (38.6)	53 (40.5)	61 (41.2)	251 (56.8)	68 (51.9)	74 (52.1)
95% CI	34.0–43.3	32.0–49.4	33.2–49.6	52.0–61.5	43.0–60.7	43.6–60.6
Any severe treatment-emergent AE, n (%)	31 (7.2)	12 (9.2)	17 (11.5)	37 (8.4)	10 (7.6)	10 (7.0)
95% CI	4.9–10.0	4.8–5.5	6.8–17.8	6.0–11.4	3.7–13.6	3.4–12.6
Any serious treatment-emergent AE, n (%)	32 (7.4)	10 (7.6)	11 (7.4)	44 (10.0)	17 (13.0)	17 (12.0)
95% CI	5.1–10.3	3.7–13.6	3.8–12.9	7.3–13.1	7.7–20.0	7.1–18.5

AE: adverse event; CI: confidence interval; HRA: high relapse activity; HRA+DAT: high relapse activity plus disease activity on treatment.

higher ARR and shorter time to first qualifying relapse and time to 6-month-confirmed EDSS worsening while on placebo. Treatment with Cladribine Tablets 3.5 mg/kg showed clear benefit in the overall population and in patients with HDA. Risk of 6-month-confirmed EDSS worsening was reduced by up to 82% in HDA subgroups of patients at increased risk of disability worsening. Analysis of

patients in these CLARITY subgroups also showed statistically significant reductions in the risk of relapses and in the time to first qualifying relapse. Importantly, the efficacy seen in patients with HDA was achieved with no additional safety concerns, supporting a positive and even better benefit:risk profile for Cladribine Tablets in this population compared with the overall population.

For patients with a high risk of future events, it is important to identify therapeutic options that can provide high levels of efficacy, preferably with an early onset of effect and without additional safety risk. Treatment with Cladribine Tablets has been previously shown to produce consistent reductions in ARR and provide an early onset of effect based on MRI assessments compared with placebo, across the spectrum of baseline demographics and disease characteristics represented in the CLARITY study.^{21,22} Previous publications from the CLARITY study have also included data on treatment outcomes with Cladribine Tablets in groups of patients using alternative definitions of HDA at baseline (≥ 2 relapses in the previous year and either ≥ 1 T1 Gd+ lesions or ≥ 9 T2 lesions at baseline).¹²

The current definitions of HRA and HRA+DAT, with utility verified through examination of their ability to identify placebo-treated patients at increased risk of relapses or EDSS worsening at the study baseline show consistency with the previous observations. They also examined a greater range of key outcomes in HDA groups compared with the earlier publication. Importantly, the use of these definitions provides a structured and systematic assessment of the effects of Cladribine Tablets, in patients who may be at an increased risk of disability worsening due to HRA or DAT. In particular, both of these simple definitions are potentially useful for routine clinical practice.

Conclusion

In the CLARITY study, patients identified with two clinically relevant HDA criteria showed clinical and MRI responses to Cladribine Tablets 3.5 mg/kg that were generally better than, or at least comparable with, the outcomes seen in the overall CLARITY study population. There were statistically significant improvements in time to 6-month-confirmed disability favouring both HDA subgroups versus patients without HDA. The safety profile of Cladribine Tablets 3.5 mg/kg in HDA patients is consistent with that described for the overall CLARITY population, supporting a positive benefit:risk profile for Cladribine Tablets in this population of patients with HDA. Therefore, treatment with Cladribine Tablets 3.5 mg/kg demonstrates significant clinical effects regardless of which highly active disease population is analysed. Treatment with Cladribine Tablets 3.5 mg/kg also led to consistent results for ARR, time to first qualifying relapse, NEDA, time to 3-month-confirmed disability worsening and MRI endpoints for patients with HDA.

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