Proportions of Patients With Highly Active RMS Achieving No Evidence of Disease Activity in Response to Cladribine Tablets in CLARITY

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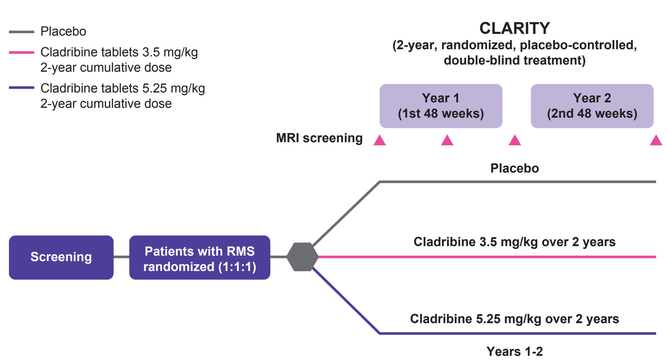
INTRODUCTION

- CLARITY, a large study (1326 patients, **Figure 1**) in patients with early and moderately advanced active relapsing multiple sclerosis (RMS), demonstrated that cladribine tablets 3.5 mg/kg, given in short courses annually over 2 years, significantly reduced relapse rates, disability worsening, and outcomes assessed by magnetic resonance imaging (MRI) versus placebo.[1]
- Patients with RMS who show an increased rate of relapse or disability progression can be described as having high disease activity (HDA). Analysis of CLARITY may provide insights into the efficacy of cladribine tablets in patients with evidence of HDA.
- The high efficacy of new treatments like cladribine tablets may warrant modification of treatment aims to go beyond reduction of relapse rates and disability progression. No evidence of disease activity (NEDA) is a composite of measures that includes no relapses, no disability worsening, and no MRI activity. Previous *post hoc* analyses have analyzed individual and composite NEDA measures in CLARITY using alternative definitions of HDA at baseline.[2]

Figure 1. CLARITY Study Design



MRI, magnetic resonance imaging; **RMS**, relapsing multiple sclerosis.

OBJECTIVE

- The aim of this *post hoc* analysis was to compare the effects of cladribine tablets 3.5 mg/kg versus placebo on the proportion of patients with NEDA in subgroups of CLARITY patients at higher risk of disease progression than the intent-to-treat (ITT) population, selected using two HDA definitions.

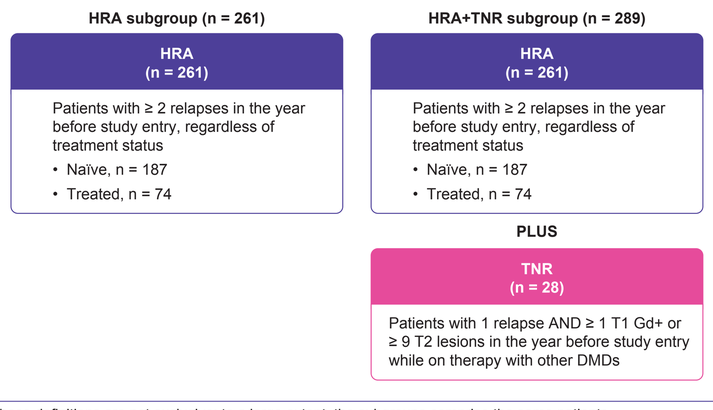
METHODS

- The CLARITY study enrolled patients aged 18–65 years with a definite diagnosis of relapsing-remitting multiple sclerosis (RRMS):[3]
  - ≥ 1 relapse in the 12 months before study entry, but no relapses within the 28 days before entry.
  - Neurological lesions detectable by MRI consistent with MS.
  - An Expanded Disability Status Scale (EDSS) score of 0−≤ 5.5.
- Patients were excluded if they had received a disease-modifying drug (DMD) within 3 months before study entry, or if treatment with > 1 DMD had failed.
- In CLARITY, MRI scans were carried out at the pre-trial assessment and at Weeks 24, 48, and 96 (or early termination).

HDA Subgroups

- CLARITY patients randomized to cladribine tablets 3.5 mg/kg (N = 433) or placebo (N = 437) were retrospectively analyzed using two different HDA definitions based on relapse history, prior treatment, and MRI characteristics.
- Two overlapping sets of criteria (**Figure 2**) were applied in the analysis of baseline disease characteristics to subdivide patients into HDA groups based upon:
  1. High relapse activity (HRA); patients with ≥ 2 relapses in the year before study entry, regardless of prior use of DMD.
  2. HRA plus treatment nonresponse (HRA+TNR); patients with ≥ 2 relapses in the year before study entry, regardless of prior use of DMD, plus patients with ≥ 1 relapse AND ≥ 1 T1 gadolinium-enhancing (Gd+) or ≥ 9 T2 lesions in the year before study entry while on DMD therapy.
- Data from the 2-year, double-blind periods of CLARITY were used to compare the efficacy of cladribine tablets versus placebo in patients with RMS in the overall population and in subgroups defined by these baseline characteristics.
- The ability of these criteria to retrospectively identify patients with HDA and the effects of cladribine tablets 3.5 mg/kg versus placebo on relapse rates and disability outcomes in these patients has been presented previously.[4,5]

Figure 2. Definitions of High Disease Activity



NB These definitions are not exclusive; to a large extent, the subgroups comprise the same patients.
DMD, disease modifying drug; **Gd+**, gadolinium-enhancing; **HRA**, high relapse activity; **HRA+TNR**, high relapse activity plus treatment nonresponse.

- All HDA analyses were *post hoc* and not pre-specified; no multiplicity adjustments were done to the resulting *P* values. Comparisons with a *P* value < 0.05 by statistical testing should be regarded as nominally significant.

NEDA

- NEDA was defined as qualifying relapse-free, 3-month confirmed EDSS progression-free, T1 Gd+ lesion-free, and active T2 lesion-free.
- The composite analysis looked at patients who achieved all components of NEDA over the full time period in CLARITY, and received treatment with cladribine tablets 3.5 mg/kg or placebo. Patients who were missing data for one or more components of NEDA were reported as unknown. Patients who withdrew early(< 83 weeks) with no disease activity were reported as unknown.
- Odds ratios (ORs) and 95% confidence intervals (95% CI) were calculated for NEDA in patients treated with cladribine tablets 3.5 mg/kg or placebo, in the ITT population and in patient subgroups, from a logistic regression with treatment as fixed effect and study as covariate.

RESULTS

- The current definitions of HRA and HRA+TNR were validated through examination of their ability to identify placebo-treated patients at increased risk of relapses or EDSS progression and show consistency with the previous observations using alternative definitions of HDA at baseline.[2]

Patients

- Demographics and disease characteristics were similar across HDA subgroups (**Table 1**). The characteristics of patients who did not fulfill the HDA criteria were also similar across the subgroups (data not shown).
- The overall analysis involved 870 patients randomized to placebo (n = 437) or cladribine tablets 3.5 mg/kg (n = 433):
  - Among the non-HRA patients, 306 received placebo and 303 received cladribine tablets 3.5 mg/kg.
  - Among the non-HRA+TNR patients, 288 received placebo and 293 received cladribine tablets 3.5 mg/kg.

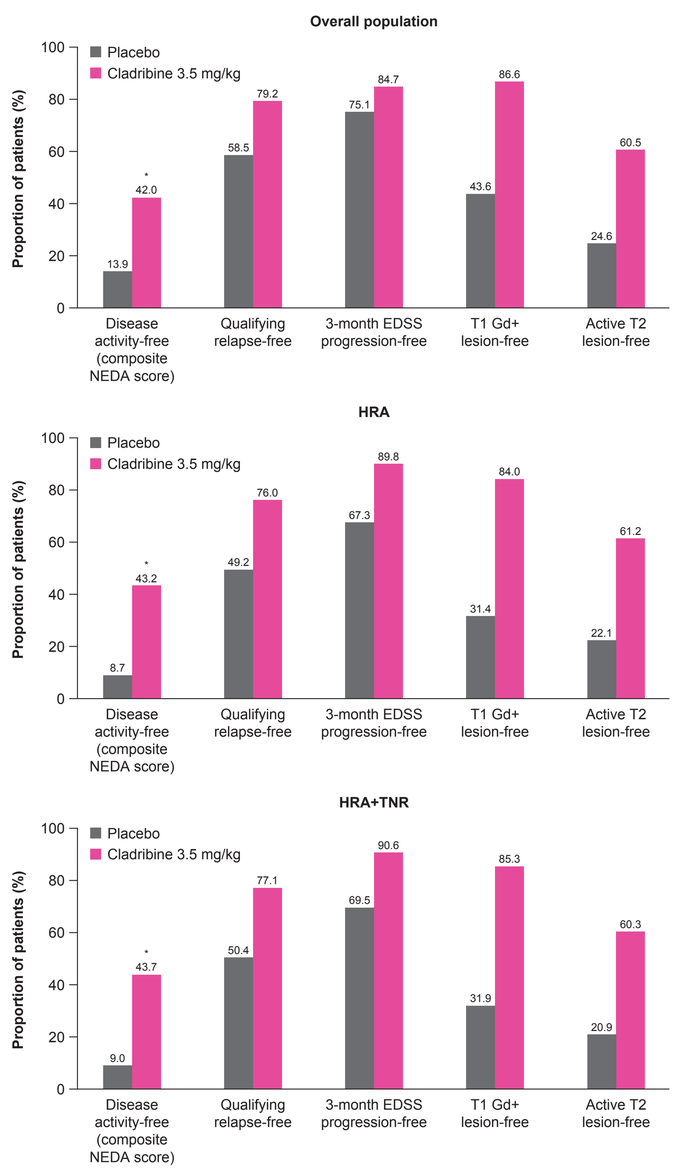
Table 1. Patient Demographics and Disease Characteristics by HDA Subgroup

	Placebo		Cladribine Tablets 3.5 mg/kg	
	HRA (n = 131)	HRA+TNR (n = 149)	HRA (n = 130)	HRA+TNR (n = 140)
Age, years; mean (SD)	36.7 (10.3)	37.1 (10.2)	36.5 (9.5)	36.3 (9.5)
Female, n (%)	82 (62.6)	94 (63.1)	96 (73.8)	102 (72.9)
Disease duration, years; mean (SD)	4.51 (5.48)	4.75 (5.34)	3.90 (5.07)	3.94 (4.92)
Prior use of DMDs, n (%)	38 (29.0)	56 (37.6)	36 (27.7)	46 (32.9)
Relapses in prior 12 months, n (%)				
0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1	0 (0.0)	18 (12.1)	0 (0.0)	10 (7.1)
2	110 (84.0)	110 (73.8)	105 (80.8)	105 (75.0)
≥ 3	21 (16.0)	21 (14.1)	25 (19.2)	25 (17.9)
EDSS score; mean (SD)	2.91 (1.37)	2.97 (1.35)	2.90 (1.33)	2.86 (1.32)
Number of T1 Gd+ lesions; mean (IQR)	1.1 (0.0;1.0)	1.0 (0.0;1.0)	1.4 (0.0;1.0)	1.3 (0.0;1.0)
Number of T2 lesions; mean (IQR)	30.0 (15.0;39.0)	29.9 (16.0;39.0)	25.3 (12.0;33.0)	25.2 (12.0;33.5)

DMD, disease modifying drug; **EDSS**, Expanded Disability Status Scale; **Gd+**, gadolinium-enhancing; **HDA**, high disease activity; **HRA**, high relapse activity; **HRA+TNR**, high relapse activity plus treatment nonresponse; **IQR**, interquartile range; **SD**, standard deviation.

Patients Who Achieved NEDA and Each Component

Figure 3. Effects of Placebo and Cladribine Tablets 3.5 mg/kg on the Proportions of Patients Who Fulfilled the Individual Components of NEDA, Excluding Unknowns



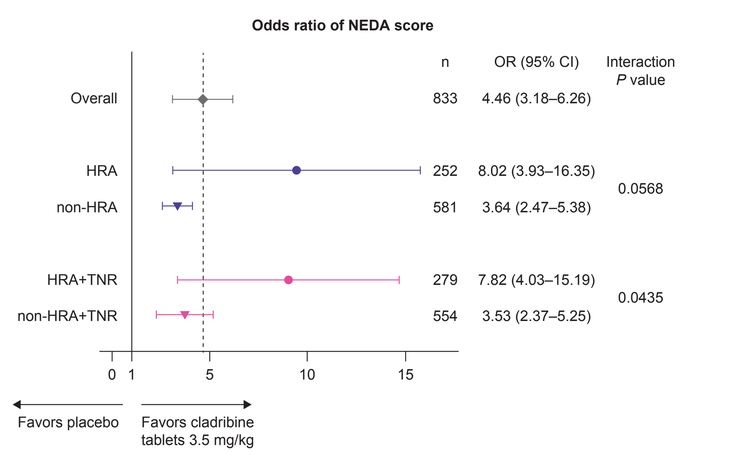
* *P* <0.0001 vs placebo.
EDSS, expanded Disability Status Scale; **Gd+**, gadolinium-enhancing; **HRA**, high relapse activity; **HRA+TNR**, high relapse activity plus treatment nonresponse; **NEDA**, no evidence of disease activity.

- In the overall CLARITY population, and in each HDA subgroup, the proportion of patients who fulfilled each component of NEDA (patients qualifying relapse-free, 3-month confirmed EDSS progression-free, T1 Gd+ lesion-free, and active T2 lesion-free) over 2 years was higher with cladribine tablets 3.5 mg/kg than placebo (**Figure 3**).
- In general, the effects of treatment with cladribine tablets 3.5 mg/kg versus placebo were similar for each HDA subgroup and the overall CLARITY population.

Odds of Achieving NEDA

- Odds ratios for achieving NEDA status in the overall population and the two HDA subgroups are shown in **Figure 4**.
  - These values were significantly more favorable than the non-HDA counterpart subgroup for the HRA+TNR definition (interaction *P* value = 0.0435).

Figure 4. Effects of Cladribine Tablets 3.5 mg/kg Versus Placebo on the Odds Ratio for Composite NEDA Score in the Overall Patient Population and in Each HDA Subgroup



CI, confidence interval; **HDA**, high disease activity; **HRA**, high relapse activity; **HRA+TNR**, high relapse activity plus treatment nonresponse; **NEDA**, no evidence of disease activity; **OR**, odds ratio.

CONCLUSIONS

- **In a large study of patients with active RMS, treatment with cladribine tablets significantly increased the proportion of HDA patients with no evidence of disease activity compared with placebo.**
- **Compared with the overall study population, each HDA subgroup showed higher odds of achieving NEDA with cladribine tablets 3.5 mg/kg versus placebo.**

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DISCLOSURES

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