Radiological Outcomes with Cladribine Tablets in High Disease Activity Subgroups of Patients with Relapsing Multiple Sclerosis in the CLARITY Study

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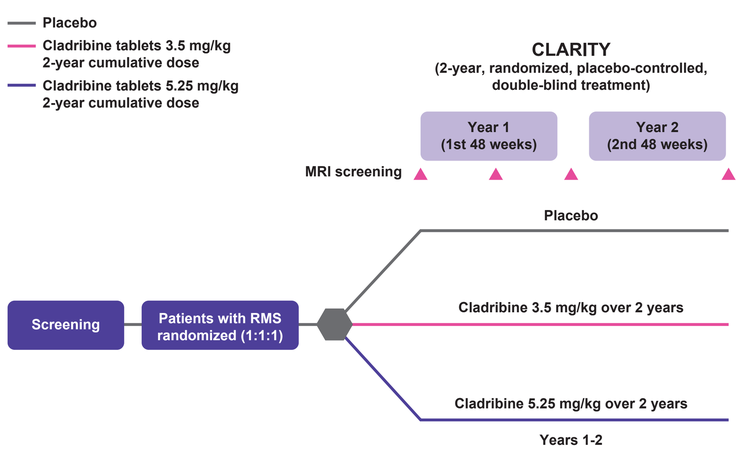
INTRODUCTION

- CLARITY was a large (1326 patients), randomized, double-blind study in patients with early and moderately advanced active relapsing multiple sclerosis (RMS) (see **Figure 1** for study design), in which treatment with cladribine tablets showed strong efficacy versus placebo (PBO) over 2 years.[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.

Figure 1. CLARITY Study Design



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

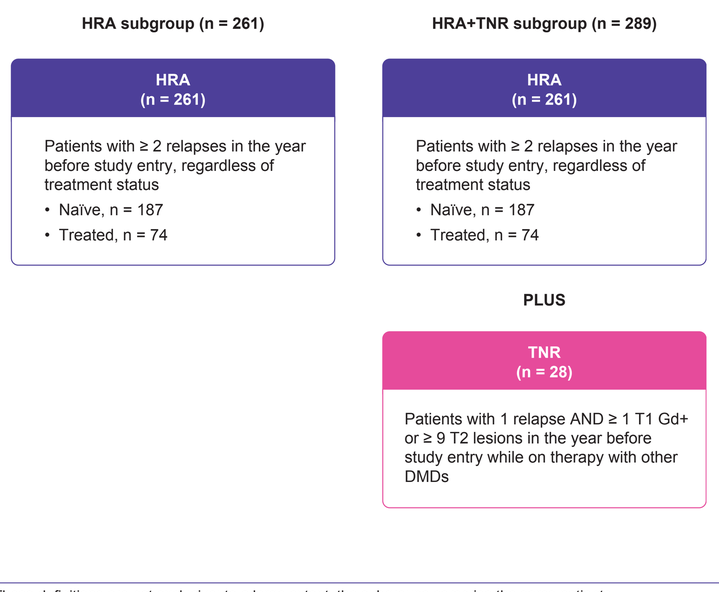
OBJECTIVE

- To compare the effects of cladribine tablets 3.5 mg/kg versus placebo on outcomes assessed by magnetic resonance imaging (MRI) in subgroups of CLARITY patients with evidence of HDA at study entry, using two HDA definitions.

METHODS

- The CLARITY study enrolled patients aged 18–65 years with a definite diagnosis of relapsing remitting multiple sclerosis (RRMS):[2]
  - ≥ 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.
- 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 (Gd+) or ≥ 9 T2 lesions in the year before study entry while on DMD therapy.
- 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.[3,4]

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.

- Efficacy analyses from CLARITY assessed the overall population and HDA subgroups and corresponding non-HDA subgroups based on cumulative numbers of new T1 Gd+ lesions, cumulative numbers of active T2 lesions, and cumulative numbers of combined unique (CU) lesions (defined as a new T1 Gd+ lesion, or a new or enlarging T2 lesion, or both, without double-counting).
- All HDA 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.

RESULTS

Patients

- Demographics and disease characteristics were similar across the subgroups of patients who met the HDA definitions (**Table 1**). The demographics and disease 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.
  - In those who did not meet the HRA+TNR criteria (i.e. non-HDA patients), 288 received placebo and 293 received cladribine tablets 3.5 mg/kg.

Table 1. Patient Demographics and Disease Characteristics by HDA Subgroup

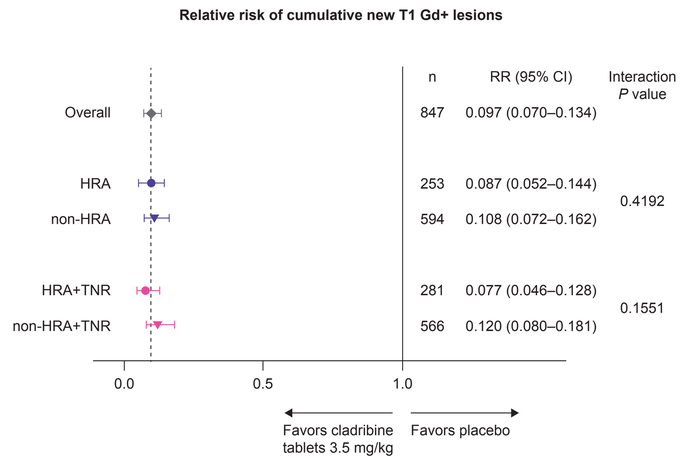
	Placebo		Cladribine Tablets 3.5 mg/kg	
	HRA (n = 131)	HRA+TNR (n = 149)	HRA (n = 130)	HRA+TNR (n = 140)
Age, years; mean (SD)	36.7 (10.3)	37.1 (10.2)	36.5 (9.5)	36.3 (9.5)
Female, n (%)	82 (62.6)	94 (63.1)	96 (73.8)	102 (72.9)
Disease duration, years; mean (SD)	4.51 (5.48)	4.75 (5.34)	3.90 (5.07)	3.94 (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.

Cumulative New T1 Gd+ Lesions

- The relative risk of cumulative new T1 Gd+ lesions for patients in both subgroups treated with cladribine tablets 3.5 mg/kg over 2 years was low, with strong effects observed in each treatment subgroup (**Figure 3**).
- This was supportive of the risk reduction seen in the overall population.
- Neither the HRA or HRA+TNR subgroups showed statistical significance versus patients who had failed to meet the respective HDA criteria (i.e. non-HRA and non-HRA+TNR patients).

Figure 3. Forest Plot of Relative Risk of Cumulative New T1 Gd+ Lesions by HDA Subgroup for Cladribine Tablets 3.5 mg/kg versus Placebo

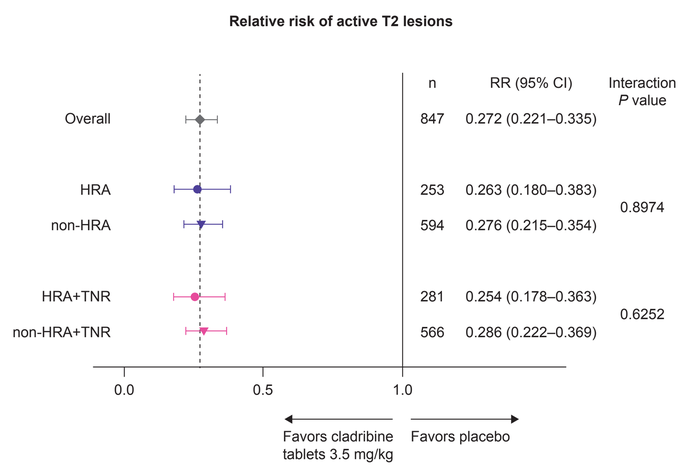


CI, confidence interval; **Gd+**, gadolinium-enhancing; **HDA**, high disease activity; **HRA**, high relapse activity; **HRA+TNR**, high relapse activity plus treatment nonresponse; **RR**, relative risk.

Active T2 Lesions

- Treatment effects were consistent in both HDA subgroups and the overall population (**Figure 4**).
- Neither the HRA or HRA+TNR subgroups showed statistical significance versus patients who had failed to meet the respective HDA criteria.

Figure 4. Forest Plot of Relative Risk of Active T2 Lesions by HDA Subgroup for Cladribine Tablets 3.5 mg/kg versus Placebo

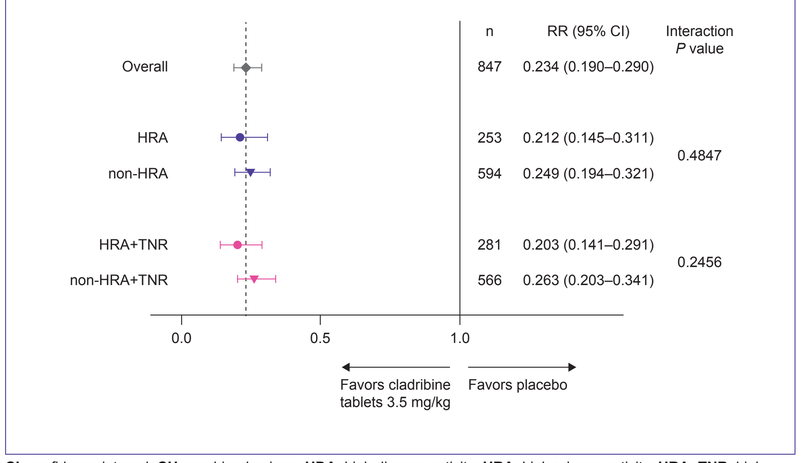


CI, confidence interval; **HDA**, high disease activity; **HRA**, high relapse activity; **HRA+TNR**, high relapse activity plus treatment nonresponse; **RR**, relative risk.

Cumulative CU Lesions

- Treatment effects were consistent in both HDA subgroups and the overall population (**Figure 5**).
- Neither the HRA or HRA+TNR subgroups showed statistical significance versus patients who had failed to meet the respective HDA criteria.

Figure 5. Forest Plot of Relative Risk of Cumulative CU Lesions by HDA Subgroup for Cladribine Tablets 3.5 mg/kg versus Placebo



CI, confidence interval; **CU**, combined unique; **HDA**, high disease activity; **HRA**, high relapse activity; **HRA+TNR**, high relapse activity plus treatment nonresponse; **RR**, relative risk.

CONCLUSIONS

- **In patients with RMS in the CLARITY study, treatment with cladribine tablets 3.5 mg/kg produced statistically significant effects versus placebo on cumulative new T1 Gd+ lesions, active T2 lesions, and cumulative CU lesions in two subgroups of patients selected using HDA criteria.**
- **In each HDA subgroup, there was a consistent treatment effect on radiological outcomes with cladribine tablets 3.5 mg/kg irrespective of disease activity before entry to the CLARITY study, or prior DMD use.**

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DISCLOSURES

GG has received speaker honoraria and consulting fees from Abbvie, Atara Bio, Almirall, Bayer Schering Pharma, Biogen Idec FivePrime, GlaxoSmithKline, GW Pharma, Merck, Pfizer Inc, Protein Discovery Laboratories, Teva Pharmaceutical Industries Ltd, Sanofi-Genzyme, UCB, Vertex Pharmaceuticals, Ironwood, and Novartis; and has received research support unrelated to this study from Biogen Idec, Merck, Novartis, and Ironwood. **KR** has received honoraria for lectures and steering committee meetings from EMD Serono, Biogen Idec, Sanofi-Aventis, Genzyme, Novartis, Teva Neurosciences, Acorda, and Roche/Genentech. **SC** has received honoraria for lectures/consultations from Merck, Bayer HealthCare, Sanofi-Aventis, Neurology Reviews, Biogen Idec, Teva Pharmaceuticals, and Actinobac Biomed Inc.; has served on advisory boards for Bayer HealthCare, Merck, Actinobac Biomed, Teva Pharmaceuticals, and Biogen Idec; and received grant support from Bayer HealthCare. **GC** has received consulting fees from Novartis, Teva Pharmaceutical Industries Ltd., Sanofi-Aventis, Merck, Receptos, Biogen Idec, Genentech-Roche, and Bayer Schering; lecture fees from Novartis, Teva Pharmaceutical Ind. Ltd., Sanofi-Aventis, Merck, Biogen Dompè, Bayer Schering, and Serono Symposia International Foundation; and trial grant support from Novartis, Teva Pharmaceutical Ind. Ltd., Sanofi-Aventis, Receptos, Biogen Idec, Genentech-Roche, Merck, Biogen Dompè, and Bayer Schering. **PR** has received honoraria for lectures/steering committee meetings from Merck, Biogen Idec, Bayer Schering Pharma, Boehringer-Ingelheim, Sanofi-Aventis, Genzyme, Novartis, Teva Pharmaceutical Industries, and Serono Symposia International Foundation. **PS-S** has served on advisory boards for Biogen, Merck, Novartis, Teva, MedDay Pharmaceuticals, and GSK; on steering committees or independent data monitoring boards in trials sponsored by Merck, Teva, GSK, and Novartis; has received speaker honoraria from Biogen Idec, Merck, Teva, Sanofi-Aventis, Genzyme, and Novartis. His department has received research support from Biogen, Merck, Teva, Novartis, Roche, and Genzyme. **PV** has received honoraria or consulting fees from Biogen, Sanofi-Genzyme, Bayer, Novartis, Merck, Celgen, Roche, and Almirall; and research support from Biogen, Sanofi-Genzyme, Bayer, and Merck. **CH** is an employee of Merck KGaA, Darmstadt, Germany. **FD** is an employee of EMD Serono, Inc., a business of Merck KGaA, Darmstadt, Germany.

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