P073

Efficacy of Cladribine Tablets on Individual Outcomes in Patients with Relapsing-Remitting Multiple Sclerosis Not Achieving NEDA Status in CLARITY

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INTRODUCTION

- The prognostic value of no evidence of disease activity (NEDA) status on long-term outcomes in multiple sclerosis (MS) is unclear[1]
- Over half of patients on currently approved therapies do not achieve NEDA status over 2 years, leading to frequent switches to different treatments[2–4]
- Cladribine tablets (3.5 mg/kg cumulative dose over 2 years) are approved for the treatment of relapsing forms of MS
  - Efficacy outcomes of cladribine tablets 3.5 mg/kg (cumulative dose over 2 years) in relapsing-remitting MS (RRMS) were shown in the pivotal Phase 3, 96-week, placebo-controlled CLARITY study[5]
    - *Post hoc* analysis of CLARITY found that the percentage of patients achieving NEDA status over 96 weeks was significantly higher in the cladribine tablets 3.5 mg/kg group (44.3%) versus the placebo group (15.8%, P<0.0001)[6]

OBJECTIVE

- This *post hoc* analysis aimed to determine whether patients who had evidence of disease activity (therefore did not achieve NEDA status) over 2 years in CLARITY still experienced treatment benefits with cladribine tablets 3.5 mg/kg versus placebo

METHODS

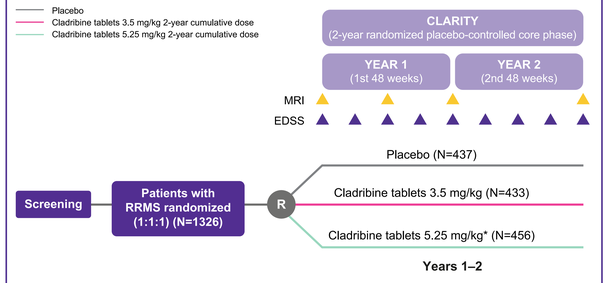
- Patients from the CLARITY study with evidence of disease were analyzed
- Inclusion criteria were disease activity in at least one of the following components at Week 96:
  - Relapse
  - 3-month confirmed disability progression (CDP; assessed by score increases in the Expanded Disability Status Scale [EDSS])
  - New lesion activity on magnetic resonance imaging (MRI; new T1 gadolinium-enhancing [Gd+] and active T2 lesions)
- The efficacy of cladribine tablets 3.5 mg/kg over the 96-week study period was compared with placebo
- All analyses were performed using SAS® software version 9.4 or higher
- This was an exploratory, *post hoc* analysis; P values below 0.05 were considered nominally significant

RESULTS

Patients

- In the CLARITY study, 1326 patients with RRMS were randomized to treatment with placebo (N=437), cladribine tablets 3.5 mg/kg (N=433) or cladribine tablets 5.25 mg/kg (N=456) (**Figure 1**)
  - Only data from patients treated with the cladribine tablets 3.5 mg/kg dose are shown as it is the approved dose
- Overall, 68.4% of patients (N=595) did not achieve NEDA status
  - The percentage of patients not achieving NEDA status was higher in the placebo group (81.2%) than in the cladribine tablets 3.5 mg/kg group (55.4%)
- Baseline characteristics of patients not achieving NEDA status were similar between the placebo and cladribine tablets 3.5 mg/kg groups, with some differences in sex, prior use of disease-modifying drugs (DMD), and no T1 Gd+ lesions (**Table 1**)

Figure 1. Design of the CLARITY Study



*Cladribine tablets 3.5 mg/kg over 2 years is the only approved dose
EDSS, Expanded Disability Status Scale; **MRI,** magnetic resonance imaging; **RRMS,** relapsing-remitting multiple sclerosis

Table 1. Baseline Demographics and Disease Characteristics of Patients Who Did Not Achieve NEDA in the CLARITY Study

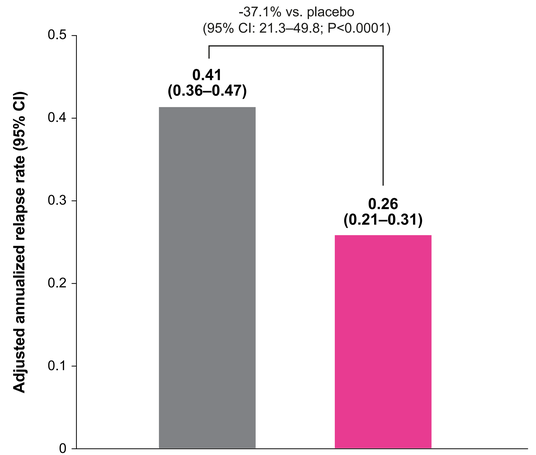
	Placebo (N=355)	Cladribine tablets 3.5 mg/kg (N=240)
Age (years), mean (SD)	37.6 (9.9)	36.5 (10.2)
Sex, n (%)		
Female	226 (63.7)	172 (71.7)
Male	129 (36.3)	68 (28.3)
Disease duration (years), mean (SD)	4.72 (4.98)	4.58 (5.62)
Prior use of DMD, n (%)	110 (31.0)	66 (27.5)
Relapses in prior 12 months, n (%)		
0	0	0
1	239 (67.3)	169 (70.4)
2	96 (27.0)	56 (23.3)
≥3	20 (5.6)	15 (6.3)
EDSS score, mean (SD)	2.89 (1.33)	2.78 (1.30)
Number of T1 Gd+ lesions, mean (SD)	0.9 (2.3)	1.3 (3.3)
Number of T1 Gd+ lesions, n (%)		
0	234 (65.9)	138 (57.5)
≥1	121 (34.1)	102 (42.5)
Number of T2 lesions, mean (SD)	27.9 (18.4)	26.9 (16.5)
Number of T2 lesions, n (%)		
<9	35 (9.9)	23 (9.6)
≥9	320 (90.1)	217 (90.4)
Volume of T2 lesions (cm³), mean (SD)	14.8 (13.6)	15.1 (15.4)

DMD, disease-modifying drug; **EDSS,** Expanded Disability Status Scale; **Gd+,** gadolinium-enhancing; **NEDA,** no evidence of disease activity; **SD,** standard deviation

Relapse Rate in Patients Who Did Not Achieve NEDA

- Compared with placebo, treatment with cladribine tablets 3.5 mg/kg significantly reduced the annualized relapse rate (P<0.0001; **Figure 2**)
- The relative risk ratio with cladribine tablets 3.5 mg/kg versus placebo was 0.63 (95% CI: 0.50–0.79)

Figure 2. Estimated Annualized Rates for Qualifying Relapses over 96 Weeks in Patients Who Did Not Achieve NEDA



Rates shown were estimated using a Poisson regression model of the relapse count as the dependent variable with fixed effect for treatment group and region and the log of time on study as offset. P values are based on the Wald Chi-square test. **CI**, confidence interval; **NEDA**, no evidence of disease activity

Time to CDP in Patients Who Did Not Achieve NEDA

- No clear differences in CDP were observed in patients who did not achieve NEDA treated with cladribine tablets 3.5 mg/kg versus placebo (data not shown)

MRI Outcomes in Patients Who Did Not Achieve NEDA

- The mean cumulative number (standard deviation) of new T1 Gd+ lesions was lower in the cladribine tablets 3.5 mg/kg group than in the placebo group (**Table 2**). The adjusted analysis showed reductions in new T1 Gd+ lesions of 85.9% versus placebo (P<0.0001)
- Numbers of active T2 lesions followed the same pattern; adjusted reduction versus placebo was 60.3% with cladribine tablets 3.5 mg/kg (P<0.0001; **Table 2**)

Table 2. Numbers of Lesions Detected at Week 96 in Patients Who Did Not Achieve NEDA

	Placebo (N=354)	Cladribine tablets 3.5 mg/kg (N=238)
Cumulative number of new T1 Gd+ lesions, mean (SD)	2.7 (4.7)	0.5 (1.1)
Adjusted mean number of new T1 Gd+ lesions (95% CI)	1.05 (0.89–1.26)	0.15 (0.11–0.20)
Percentage reduction vs. placebo (95% CI)	–	85.9 (80.5–89.8)
P value vs. placebo	–	<0.0001
Cumulative number of active T2 lesions, mean (SD)	4.4 (5.3)	1.7 (2.1)
Adjusted mean number of active T2 lesions (95% CI)	1.60 (1.43–1.79)	0.64 (0.55–0.74)
Percentage reduction vs. placebo (95% CI)	–	60.3 (52.2–66.9)
P value vs. placebo	–	<0.0001

Adjusted data were calculated using a Negative Binomial regression model with fixed effect for treatment group, region and number of T1 lesions at baseline, and with the log of number of scan as the offset. P values are based on the Wald Chi-square test
CI, confidence interval; **Gd+,** gadolinium-enhancing; **NEDA,** no evidence of disease activity; **SD,** standard deviation

CONCLUSION

- **This 96-week study shows that in patients with RRMS not achieving NEDA status, treatment with cladribine tablets still provides nominally significant reductions in the risk of relapse and active MRI lesions versus placebo**

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