P071

The CLARITY Study: Efficacy Outcomes Among Patients who Received Disease-Modifying Drugs Prior to Treatment with Cladribine Tablets

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INTRODUCTION

- Cladribine tablets 10 mg (cumulative dose 3.5 mg/kg over 2 years) are a recent addition to the treatment options for relapsing forms of multiple sclerosis (MS)[1,2]
- The CLARITY study showed that cladribine tablets 3.5 mg/kg resulted in improved efficacy outcomes versus placebo in patients with relapsing-remitting MS (RRMS)[3]
  - A 57.6% lower annualized relapse rate (ARR) at Week 96 with cladribine tablets 3.5 mg/kg versus placebo (P<0.001)
  - *Post hoc* recalculation found a 41% reduction in time to 3-month sustained change in disability versus placebo (hazard ratio [HR] 0.59; 95% confidence interval [CI]: 0.43–0.82; P=0.0016)[4]
  - A 47% reduction in time to 6-month sustained change in disability versus placebo (HR 0.53; 95% CI: 0.36–0.79; P=0.0016)[4]
- Patients with RRMS are often treated with disease-modifying drugs (DMDs). If there is a poor treatment response to a DMD, adherence challenges or tolerability issues, treatment switching may improve outcomes[5]
- Patients who previously received treatment may have a greater risk of relapse or disease-worsening in comparison to treatment-naïve patients[6]
- The impact of prior DMD use on the efficacy of cladribine tablets is unknown
  - The incidence of lymphopenia was shown to be greater in patients who had received DMDs for relapsing forms of MS prior to study entry, compared to those with no prior DMD use[2]
- Therefore it is relevant to investigate efficacy in patients treated with cladribine tablets who have a history of DMD treatments

OBJECTIVES

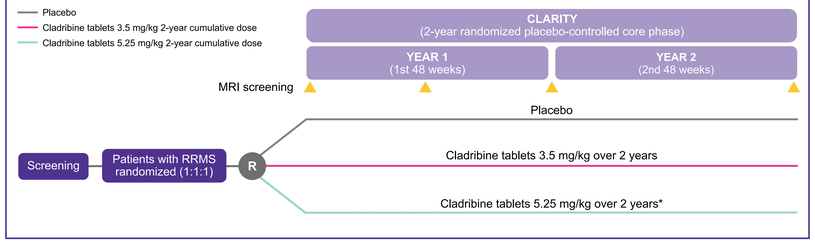
- *Post hoc* analysis to investigate efficacy outcomes in the sub-group of patients who had used a DMD at any time prior to randomization in CLARITY. Efficacy outcomes included:
  - Clinical outcomes
  - Magnetic resonance imaging (MRI) lesion counts

METHODS

The CLARITY Study

- CLARITY was a multicenter, double-blind, randomized, placebo-controlled Phase 3 study in patients with RRMS (**Figure 1**)
- The design and methodology have been described previously[3]
- CLARITY included patients treated with ≤ 2 DMDs prior to study entry
  - Patients treated with > 2 DMDs were excluded from the study

Figure 1. CLARITY Study Design



*The only approved dose is 3.5 mg/kg over 2 years.
MRI, magnetic resonance imaging; **R**, randomization; **RRMS**, relapsing-remitting multiple sclerosis

Efficacy Outcomes

- Analyses of efficacy were stratified by the cohort of patients who had received a prior DMD treatment at any time before entering CLARITY. Endpoints included:
  - ARR and relapse free rate (qualifying relapses as defined in the CLARITY study)[3]
  - MRI activity (cumulative active T2, combined unique, new T1 hypointense and T1 gadolinium enhancing [Gd+] lesions)
  - Time to 3-month and 6-month confirmed expanded disability status scale (EDSS) progression (CDP)

Statistical Analyses

- A *post hoc* analysis was conducted on the subgroup of CLARITY patients who received prior DMDs. The study group, which received the marketed authorization dose, 3.5 mg/kg was included in this analysis[1,2]
- Continuous variables were summarized using descriptive statistics, i.e. number of subjects (N), number of subjects with non-missing values, mean, standard deviation (± SD) and median. Qualitative variables were summarized by counts and percentages
- No adjustment for multiplicity and no adjustments for covariates were applied in the statistical models. All statistical tests were two-sided using a significance level of 5%. As this is a *post hoc* analysis, P values <0.05 were considered nominally significant

RESULTS

Baseline Characteristics in Patients Who Received Prior DMDs

- In CLARITY, a total of 433 patients were randomized to cladribine tablets 3.5 mg/kg and 437 to placebo
  - Of those patients who received prior DMD, 110 were randomized to cladribine tablets 3.5 mg/kg, 132 to placebo (**Table 1**)
- The most commonly used prior DMDs were intramuscular interferon beta (IFNβ)-1a, subcutaneous (sc) IFNβ-1b, sc IFNβ-1a and sc glatiramer acetate, as previously reported in CLARITY[3]

Table 1. Baseline Demographics in Patients Who Received Prior DMDs

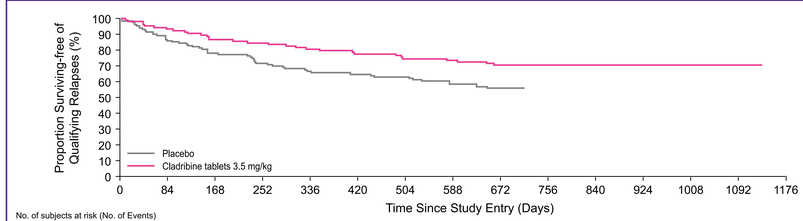
	Placebo N=132	Cladribine tablets 3.5 mg/kg N=110
Females, n (%)	87 (65.9)	88 (80.0)
Age, years, mean ± SD	37.9 ± 9.3	37.8 ± 8.9
Median EDSS	3	2.5
Disease duration, years, mean ± SD	7.32 ± 4.40	6.51 ± 4.93
Number of T1 hypointense lesions, mean ± SD	0.8 ± 1.7	0.8 ± 1.9
Number of T2 lesions, mean ± SD	29.7 ± 18.6	26.3 ± 17.2

EDSS, expanded disability status scale; **SD**, standard deviation

Qualifying Relapses in Patients Who Received Prior DMDs

- Treatment with cladribine tablets 3.5 mg/kg resulted in a 47.8% reduction in ARR compared to placebo (P<0.005)
  - Cladribine tablets 3.5 mg/kg, ARR=0.22 (95% CI: 0.16, 0.30); placebo, 0.42 (95% CI: 0.34, 0.51)
- The percentage of patients remaining relapse free was greater with cladribine tablets 3.5 mg/kg (70.4% [95% CI: 60.4, 78.3]) than with placebo (55.9% [95% CI: 46.5, 64.2]); HR 0.59 (95% CI: 0.38, 0.92; P=0.0204) (**Figure 2**)

Figure 2. Time to First Qualifying Relapse in Patients Who Received Prior DMDs



No. of subjects at risk (No. of Events)

Placebo	132(0)	109(18)	97(28)	86(36)	78(42)	75(44)	72(46)	65(51)	19(54)	0(54)	0(54)	0(54)	0(54)	0(54)	0(54)
Cladribine tablets 3.5 mg/kg	110(0)	98(7)	88(14)	85(16)	80(20)	76(23)	73(26)	72(27)	34(30)	6(30)	2(30)	2(30)	1(30)	1(30)	0(30)

Disability Progression in Patients Who Received Prior DMDs

- Risk of CDP was numerically lower in the cladribine tablets 3.5 mg/kg group versus placebo at both 3-months (HR 0.64 [95% CI: 0.35, 1.19]; P=0.16) and 6-months (HR 0.62 [95% CI: 0.30, 1.30], P=0.21), although these differences did not reach significance
- Proportion of patients who were disability progression-free was greater with cladribine tablets 3.5 mg/kg than placebo:
  - 3-months: 84.1% versus 77.1%
  - 6-months: 89.1% versus 83.7%

MRI Outcomes in Patients Who Received Prior DMDs

- Treatment with cladribine tablets 3.5 mg/kg significantly reduced brain lesion counts (P<0.001 for each type of lesion) compared with placebo (**Table 2**)
- The proportion of patients with T1 Gd+ lesions was reduced in the cladribine tablets 3.5 mg/kg group versus placebo:
  - At Week 48, percentages of patients lesion free were 82.7% and 41.7%, respectively
  - At Week 96, percentages of patients lesion free were 69.1% and 34.8%, respectively

Table 2. MRI Lesion Counts in Patients Who Received Prior DMDs

	Placebo N=132	Cladribine tablets 3.5 mg/kg N=110
Cumulative active T2 lesions		
Number of lesions, mean ± SD	4.22 ± 5.27	1.18 ± 2.02
Adjusted mean (95% CI)	1.58 (1.27, 1.97)	0.42 (0.32, 0.56)
Percentage reduction (95% CI)	73.3 (61.7, 81.4)	
Rate ratio (95% CI)	0.27 (0.19, 0.38)	
P value	< 0.0001	
Cumulative combined unique lesions		
Number of lesions, mean ± SD	5.18 ± 6.68	1.26 ± 2.15
Adjusted mean (95% CI)	1.95 (1.56, 2.45)	0.45 (0.34, 0.60)
Percentage reduction (95% CI)	76.9 (66.6, 84.0)	
Rate ratio (95% CI)	0.23 (0.16, 0.33)	
P value	< 0.0001	
Cumulative new T1 hypointense lesions		
Number of lesions, mean ± SD	1.37 ± 2.18	0.50 ± 1.23
Adjusted mean (95% CI)	0.51 (0.38, 0.69)	0.18 (0.12, 0.27)
Percentage reduction (95% CI)	64.2 (40.9, 78.3)	
Rate ratio (95% CI)	0.36 (0.22, 0.59)	
P value	< 0.0001	

CI, confidence interval; **MRI**, magnetic resonance imaging; **SD**, standard deviation

CONCLUSIONS

- **Patients who received prior DMD treatment and were treated with cladribine tablets 3.5 mg/kg showed significant improvements in relapse rates and MRI outcomes compared to prior DMD patients who received placebo**
- **These data further support a consistent effect of cladribine tablets across a broad range of patients, including patients who have used other DMDs**

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DISCLOSURES

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