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Efficacy Outcomes in Cladribine Tablets-Treated Patients in CLARITY were Similar between Patients Who Did Versus Did Not Enter CLARITY Extension

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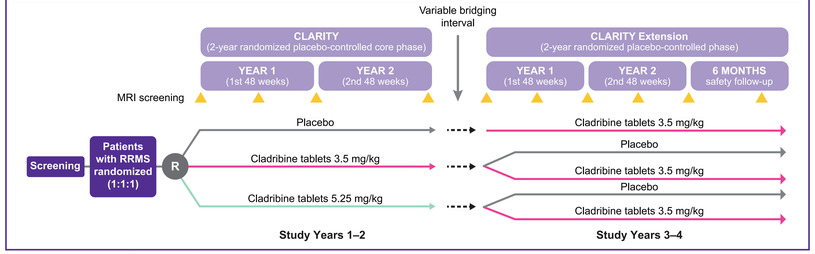
BACKGROUND

- Patients with relapsing-remitting multiple sclerosis (RRMS) treated with cladribine tablets 10 mg (3.5 mg/kg or 5.25 mg/kg cumulative dose over 2 years) in CLARITY[1] were re-randomized 2:1, with blind maintained, to receive further cladribine tablets or placebo in the CLARITY Extension study[2] (CLARITY EXT; **Figure 1**)
  - In the CLARITY EXT study, safety was the primary objective and sustained efficacy was evaluated as an exploratory endpoint
    - Treatment with cladribine tablets in Years 1 and 2 of the CLARITY study resulted in sustained efficacy, without additional active treatment, in Years 3 and 4 of the CLARITY EXT study[2]
- One potential confounding factor with any extension study is that enrolled patients could be a non-representative sample of those who started the core study, due to non-random discontinuation (through retention of certain patients, e.g. patients with specific baseline characteristics or responders to treatment)

Figure 1. CLARITY and CLARITY EXT Study Design



MRI, magnetic resonance imaging; **R,** randomization; **RRMS,** relapsing-remitting multiple sclerosis

OBJECTIVES

- The objectives of this retrospective analysis were to assess two areas of potential selection bias that could confound interpretation of efficacy results from CLARITY EXT:
  - Patients with specific disease characteristics at baseline in CLARITY
  - Patients with a greater treatment response to cladribine tablets during CLARITY

METHODS

- Selected key baseline characteristics, clinical efficacy, and outcomes on magnetic resonance imaging (MRI) over 96 weeks in CLARITY were compared for placebo-, cladribine tablets 3.5 mg/kg-, and cladribine tablets 5.25 mg/kg-treated patients who entered versus did not enter CLARITY EXT
  - Only CLARITY patients who entered CLARITY EXT and were randomized to treatment were included in the analysis. For simplicity, these patients are referred to as 'patients who entered CLARITY EXT' in this presentation
- Analyses were conducted retrospectively using descriptive statistics

RESULTS

Patients

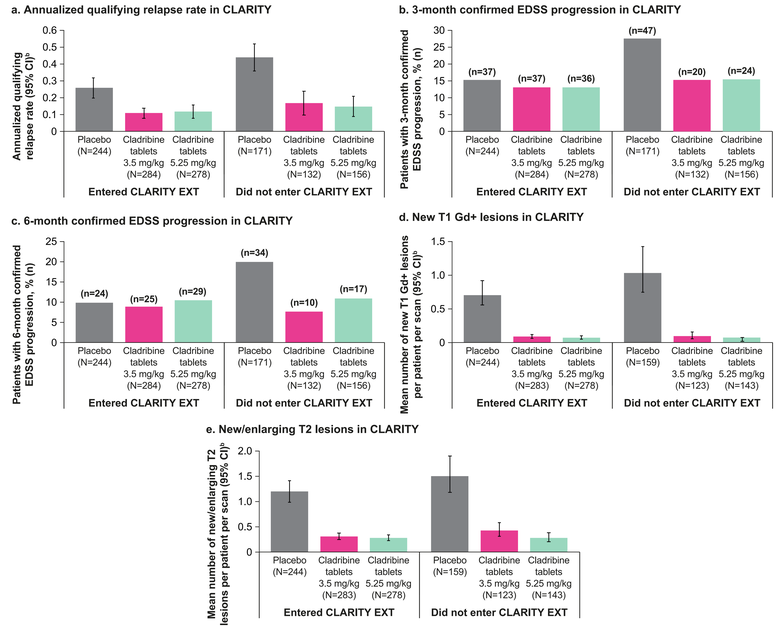
- The baseline characteristics of patients in CLARITY, grouped by those who entered versus did not enter CLARITY EXT, are shown in **Table 1**
  - Most baseline characteristics of the patients in CLARITY were similar between those who entered versus did not enter the extension study, however:
    - Independent of the treatment received in CLARITY, patients who did not enter CLARITY EXT had slightly longer disease duration (~0.7 years) and mean Expanded Disability Status Scale (EDSS) score at CLARITY baseline versus patients who entered CLARITY EXT
      - Patients treated with cladribine tablets 3.5 mg/kg in CLARITY who did not enter CLARITY EXT had higher prior use of disease-modifying drugs (DMD) prior to enrollment in CLARITY versus those who entered CLARITY EXT

Table 1. Baseline Characteristics of Patients in CLARITY, Grouped by Those Who Entered[a] versus Did Not Enter CLARITY EXT

Randomized treatment in CLARITY	Entered CLARITY EXT (N=806)[a]			Did not enter CLARITY EXT (N=459)		
	Placebo (N=244)	Cladribine tablets 3.5 mg/kg (N=284)	Cladribine tablets 5.25 mg/kg (N=278)	Placebo (N=171)	Cladribine tablets 3.5 mg/kg (N=132)	Cladribine tablets 5.25 mg/kg (N=156)
Age (years), mean (SD)	39.0 (9.6)	38.0 (10.5)	38.6 (9.9)	38.5 (10.3)	37.7 (9.9)	39.7 (9.6)
Female, %	63.9	67.3	66.2	70.8	71.2	70.5
Disease duration (years), mean (SD)	4.82 (4.81)	4.36 (5.11)	4.86 (5.0)	5.68 (6.25)	5.09 (5.66)	5.43 (5.79)
Prior use of DMD, %	29.1	21.5	29.9	31.0	34.1	30.1
EDSS score, mean (SD)	2.81 (1.29)	2.79 (1.24)	2.92 (1.32)	3.15 (1.35)	2.93 (1.27)	3.10 (1.41)
Number of T1 Gd+ lesions, mean (SD)	0.9 (2.4)	1.1 (3.1)	1.0 (2.3)	0.7 (1.6)	0.9 (1.9)	0.9 (2.1)
T2 lesion volume (cm^3), mean (SD)	13.49 (12.80)	15.73 (17.32)	17.39 (18.31)	14.77 (13.13)	13.67 (14.53)	16.95 (16.05)

[a]Only patients who were randomized to treatment in CLARITY EXT were included in the analysis
CLARITY EXT, the CLARITY extension study; **DMD,** disease modifying drug; **EDSS,** Expanded Disability Status Scale; **Gd+,** gadolinium-enhancing; **SD,** standard deviation

Figure 2. Clinical and MRI Outcomes in CLARITY for Patients Who Entered[a] versus Did Not Enter CLARITY EXT



[a]Only patients who were randomized to treatment in CLARITY EXT were included in the analysis; [a]95% confidence intervals were not adjusted for multiplicity and should be considered nominal only
CI, confidence interval; **CLARITY EXT,** the CLARITY extension study; **EDSS,** Expanded Disability Status Scale; **Gd+,** gadolinium-enhancing

Clinical Efficacy and MRI Outcomes in CLARITY as Potential Confounding Factors in CLARITY EXT

- Key clinical efficacy and MRI outcomes in CLARITY, for patients who entered versus did not enter CLARITY EXT, are shown in **Figure 2**
- Efficacy outcomes for cladribine tablets 3.5 mg/kg- or 5.25 mg/kg-treated patients in CLARITY were generally comparable between those who did versus did not enter CLARITY EXT
  - While a trend towards a slightly lower annualized qualifying relapse rate in CLARITY was observed for patients treated with cladribine tablets who entered versus did not enter CLARITY EXT (0.11 vs. 0.17, **Figure 2a**); an absolute annualized relapse rate difference of 0.06 (translating to one additional relapse over ~17 years) is not considered clinically meaningful
- Placebo-treated patients who entered CLARITY EXT had lower annualized relapse rate, number of new T1 Gd+ and new/enlarging T2 lesions, and rate of 3- and 6-month confirmed progression on EDSS in CLARITY

CONCLUSIONS

- **In CLARITY, the baseline disease characteristics of patients treated with cladribine tablets who did versus did not enter CLARITY EXT were generally similar, with overlapping confidence intervals, suggesting CLARITY EXT did not preferentially enroll patients with less severe disease at CLARITY baseline**
  - **However, slightly longer disease duration, slightly higher EDSS score, and a higher rate of prior use of disease-modifying drugs were observed in patients who did not enter CLARITY EXT versus those who did**
- **Efficacy outcomes in CLARITY were generally similar (i.e. overlapping confidence intervals) in patients treated with cladribine tablets who did versus did not enter CLARITY EXT, suggesting that CLARITY EXT did not preferentially enroll patients with a greater treatment response to cladribine tablets during CLARITY**
- **These results may assist in the interpretation of durability of efficacy outcomes from CLARITY and the CLARITY Extension study**

REFERENCES

1. Giovannoni G, et al. *N Engl J Med.* 2010;362:416–26.
2. Giovannoni G, et al. *Mult Scler.* 2018;24:1594–1604.

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