Reduction of Risk of Secondary Progressive Multiple Sclerosis Within Two Years of Treatment with Cladribine Tablets: An Analysis of the CLARITY Study

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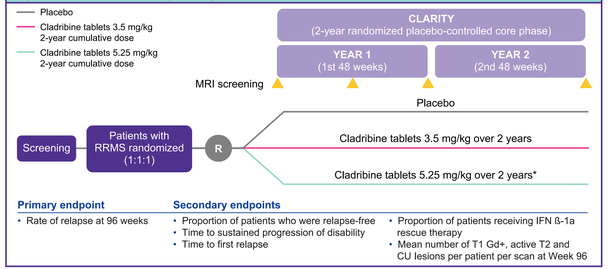
INTRODUCTION

- Cladribine tablets 10 mg (cumulative dose 3.5 mg/kg over 2 years, henceforth referred to as cladribine tablets 3.5 mg/kg) are one of the more recent additions to the treatment armamentarium for relapsing forms of multiple sclerosis (MS)[1,2]
- In the CLARITY study (**Figure 1**), cladribine tablets 3.5 mg/kg demonstrated marked efficacy versus placebo in a large cohort of patients with relapsing-remitting MS (RRMS)[3]
  - The annualized relapse rate (ARR) at Week 96 was 57.6% lower with cladribine tablets 3.5 mg/kg than for placebo ($P < 0.001$)
  - There was a 33% reduction versus placebo in time to 3-month sustained change in disability (hazard ratio [HR] 0.67; 95% confidence interval [CI] 0.48–0.93; $P = 0.02$)
  - A 47% reduction versus placebo in time to 6-month sustained change in disability was also observed (HR 0.53; 95% CI 0.36–0.79; $P = 0.0016$)[4]
- There is no agreed consensus of secondary progressive MS (SPMS) diagnosis, therefore a retrospective diagnosis must be made based on a defined minimum level of disability, characterized by irreversible disability progression that is independent of relapse[5]
  - Cladribine tablets 3.5 mg/kg may lower the risk of MS patients developing SPMS by reducing disability progression[3]

Figure 1. CLARITY Study Design



*The only approved dose is 3.5 mg/kg over 2 years.
CU, combined unique; **Gd+,** gadolinium-enhancing; **IFN,** interferon; **MRI,** magnetic resonance imaging; **R,** randomization; **RRMS,** relapsing-remitting multiple sclerosis.

OBJECTIVE

- *Post hoc* evaluation of CLARITY assessing the risk of:
  - Progression to proxy SPMS
  - Progression to Expanded Disability Score Scale (EDSS) ≥ 6.0

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]
- Patients were required to have had a relapse in the year prior to enrollment to be eligible for the study[3]

Post Hoc Analysis Population

- Patients in the intent-to-treat population randomized to either placebo or cladribine tablets 3.5 mg/kg were included in this analysis
- For endpoints with EDSS ≥ 6, additional inclusion criteria included baseline EDSS ≤ 5.5 and at least one EDSS value post-baseline

Proxy Evaluation of SPMS

- Progression to SPMS was not recorded during CLARITY
- Therefore, a proxy definition was used for SPMS, requiring all of the following conditions to be met for 3 months (83 days), with no relapse (scores within 30 days of a prior relapse were excluded):[5]
  - Confirmed disease progression (CDP; EDSS increase ≥ 1 step)
  - CDP including confirmation within the leading functional system (FS) score
  - EDSS post-baseline score ≥ 4.0
  - Pyramidal FS score ≥ 2

Efficacy Outcomes

- Patients reaching SPMS, evaluated using a proxy definition of SPMS
- Patients reaching at least one EDSS score of ≥ 6.0 post-baseline
- Patients with 3- or 6-month CDP with EDSS ≥ 6.0

Statistical Analysis

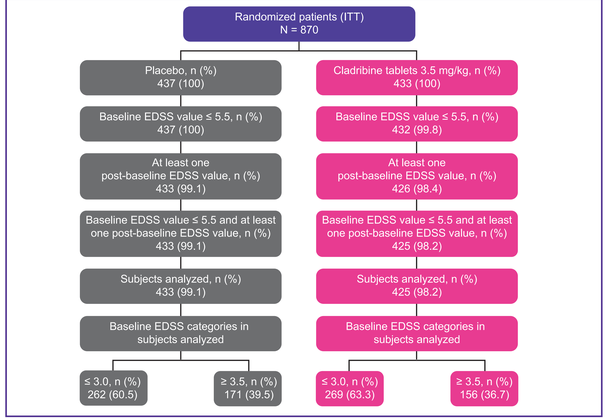
- Patients were stratified into subgroups based on baseline EDSS:
  - Baseline EDSS ≤ 3.0
  - Baseline EDSS ≥ 3.5
- Odds ratios (OR) and corresponding 95% confidence intervals (CI) were estimated by a logistic regression model with treatment and baseline EDSS (≤ 3.0 or ≥ 3.5) as fixed effects
- Patients who withdrew early (less than 587 days) before experiencing the event were considered 'unknown' and are therefore excluded from the analysis
- All analyses were performed *post hoc* without any adjustment for multiple testing and *P* values should be considered exploratory only

RESULTS

Baseline Characteristics

- Of the patients randomized in CLARITY (placebo, n = 473; cladribine tablets 3.5 mg/kg, n = 433), > 98% were eligible for inclusion in this analysis (**Figure 2**)

Figure 2. Characteristics of CLARITY Patient Population Included in Analysis

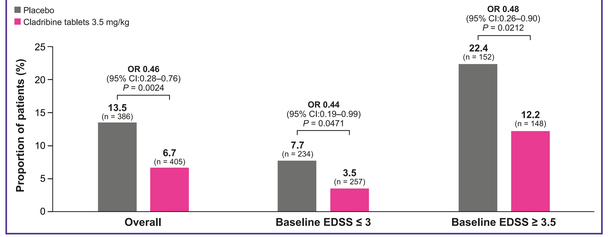


CI, confidence interval; **EDSS,** Expanded Disability Score Scale; **ITT,** intent-to-treat; **OR,** odds ratio.

Proportion of Patients with Proxy SPMS

- Overall, significantly fewer patients treated with cladribine tablets 3.5 mg/kg in CLARITY developed proxy SPMS, compared with placebo; this was also true for patients with EDSS ≤ 3.0 and EDSS ≥ 3.5 (**Figure 3**)
  - Percentage reductions for the overall and subgroups were 54%, 56% and 52%, respectively

Figure 3. Proportion of Patients Treated with Cladribine Tablets 3.5 mg/kg or Placebo Reaching Proxy SPMS in CLARITY (Week 96)

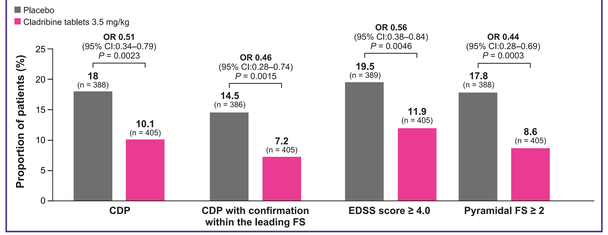


CI, confidence interval; **EDSS,** Expanded Disability Score Scale; **OR,** odds ratio.

Proportion of Patients with Individual Components of Proxy SPMS

- There was a significant reduction in the proportion of patients within each individual component of proxy SPMS when treated with cladribine tablets 3.5 mg/kg compared with placebo (**Figure 4**)
  - Percentage reduction for CDP component was 49%
  - Percentage reduction for CDP with confirmation within the leading FS was 54%
  - Proportion of patients with EDSS score ≥ 4.0 was reduced by 44% and patients with pyramidal FS ≥ 2 was reduced by 56%

Figure 4. Proportion of Patients Treated with Cladribine Tablets 3.5 mg/kg or Placebo Achieving Individual Components of Proxy SPMS in CLARITY (Week 96)

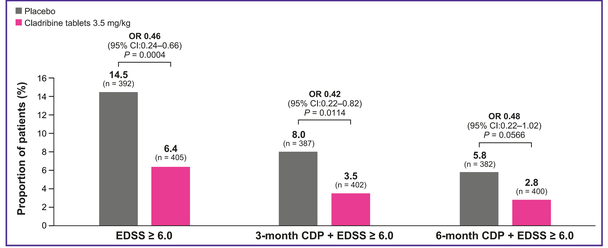


CDP, confirmed disease progression; **CI,** confidence interval; **EDSS,** Expanded Disability Score Scale; **FS,** functional score; **OR,** odds ratio.

Proportion of Patients with EDSS ≥ 6.0

- Fewer patients treated with cladribine tablets 3.5 mg/kg in CLARITY had ≥ 1 post-baseline EDSS ≥ 6.0, than the placebo group, including those with either 3- or 6-month confirmed progression (**Figure 5**)
  - Overall, significantly fewer patients reached EDSS ≥ 6.0 or 3-month CDP with EDSS ≥ 6.0 when treated with cladribine tablets 3.5 mg/kg compared with placebo. However, this significance was not observed in patients with 6-month CDP with EDSS ≥ 6.0
  - Percentage reductions were 54% for EDSS ≥ 6.0, 58% 3-month CDP with EDSS ≥ 6.0 and 52% 6-month CDP with EDSS ≥ 6.0

Figure 5. Proportion of Patients with 3- or 6-Month Confirmed Progression With EDSS ≥ 6.0 in CLARITY (Week 96)



CDP, confirmed disease progression; **CI,** confidence interval; **EDSS,** Expanded Disability Score Scale; **OR,** odds ratio.

CONCLUSIONS

- **Compared with placebo, significantly fewer patients treated with cladribine tablets 3.5 mg/kg progressed to SPMS, as measured by proxy SPMS definition**
- **Reduction in risk of reaching proxy SPMS was consistent regardless of baseline disability status (EDSS score ≤ 3 or ≥ 3.5) and was observed for all individual components of the proxy definition of SPMS**
- **Cladribine tablets 3.5 mg/kg also significantly reduced the risk of progression to EDSS ≥ 6.0 confirmed by 3-month CDP**

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DISCLOSURES

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