DXT58

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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CONCLUSIONS

Compared with placebo, significantly fewer patients treated with cladribine tablets 3.5 mg/kg progressed to SPMS, as measured by proxy SPMS definition

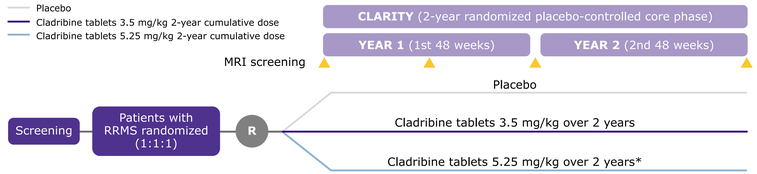
Reduction in risk of reaching proxy SPMS was consistent regardless of baseline disability status (EDSS score ≤3 or ≥3.5) and was observed for all individual components of the proxy definition of SPMS

Cladribine tablets 3.5 mg/kg also significantly reduced the risk of progression to EDSS ≥6.0 confirmed by 3-month CDP

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 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 RRMS[3]
  - The 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 (HR 0.67; 95% 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 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



Primary endpoint
- Rate of relapse at 96 weeks

Secondary endpoints
- Proportion of patients who were relapse-free
- Time to sustained progression of disability
- Time to first relapse
- Proportion of patients receiving IFN ß-1a rescue therapy
- Mean number of T1 Gd+, active T2 and CU lesions per patient per scan at Week 96

*The only approved dose is 3.5 mg/kg over 2 years.

OBJECTIVES

- *Post hoc* evaluation of CLARITY assessing the risk of:
  - Progression to proxy SPMS
  - Progression to 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 ITT 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

METHODS (cont.)

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]
  - CDP (EDSS increase ≥1 step)
  - CDP including confirmation within the leading 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

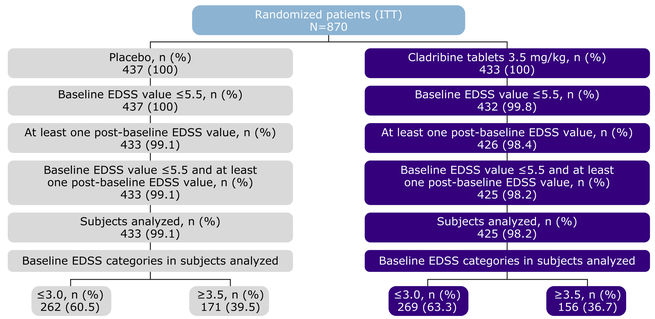
- Patients were stratified into subgroups based on baseline EDSS:
  - Baseline EDSS ≤3.0
  - Baseline EDSS ≥3.5
- OR and corresponding 95% CI were estimated by a logistic regression model with treatment and baseline EDSS (≤3.0 or ≥3.5) as fixed effects
- Patients who withdrew early (less than 587 days) 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

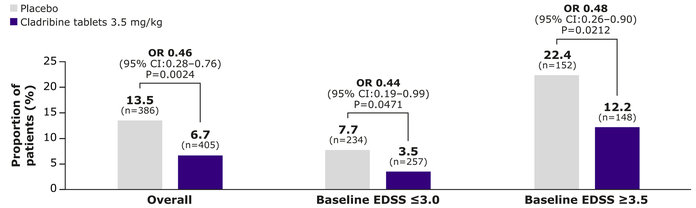


RESULTS (cont.)

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

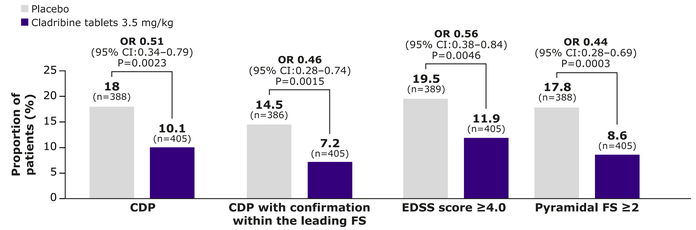
Figure 3. Proportion of Patients Treated with Cladribine Tablets 3.5 mg/kg or Placebo Reaching Proxy SPMS in CLARITY (Week 96)



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%

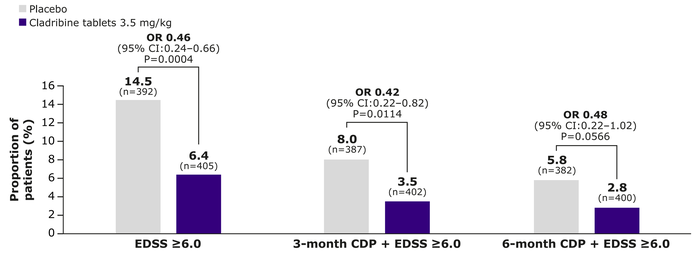
Figure 4. Proportion of Patients Treated with Cladribine Tablets 3.5 mg/kg or Placebo Achieving Individual Components of Proxy SPMS in CLARITY (Week 96)



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)



Abbreviations: ARR, annualized relapse rate; **CDP,** confirmed disease progression; **CI,** confidence interval; **CU,** combined unique; **EDSS,** Expanded Disability Score Scale; **FS,** functional system; **Gd+,** gadolinium-enhancing; **HR,** hazard ratio; **IFN,** interferon; **ITT,** intent-to-treat; **MRI,** magnetic resonance imaging; **MS,** multiple sclerosis; **OR;** odds ratio; **R,** randomization; **RRMS,** relapsing-remitting MS; **SPMS,** secondary progressive MS

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CLARITY: NCT00213135

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