P058

# Effectiveness of Cladribine Tablets in Patients with Relapsing-Remitting Multiple Sclerosis with Baseline EDSS ≥3.5 or ≤3.0 in CLARITY

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## INTRODUCTION

- Despite availability of effective treatments, approximately half of all patients with relapsing-remitting multiple sclerosis (RRMS) develop secondary progressive multiple sclerosis (SPMS) within 15 years,[1] a disease stage that leads to progressive accumulation of unremitting disability
- In recent Phase 3 trials, which used an Expanded Disability Status Scale (EDSS) score of ≥3 to define active SPMS, disease-modifying drugs showed only slight or moderate effects in delaying disability progression in patients with active SPMS[2,3]
- Cladribine tablets 10 mg (3.5 mg/kg cumulative dose over 2 years) are approved in the United States for the treatment of relapsing forms of multiple sclerosis, i.e. RRMS and active SPMS[4]
- In the 96-week CLARITY study in RRMS, treatment with cladribine tablets 10 mg (3.5 mg/kg or 5.25 mg/kg cumulative dose over 2 years) was associated with significant reductions in annualized relapse rate (ARR; P<0.001), time to 3-month confirmed disability progression (CDP; P≤0.03), and lesion activity on brain magnetic resonance imaging (MRI; all P<0.001) versus placebo[5]
- However, the efficacy of cladribine tablets has not been fully characterized according to whether patients transition to active SPMS, for which EDSS scores of ≥3.5 can be used as a proxy definition

## OBJECTIVE

- This *post hoc* analysis aimed to examine differences between cladribine tablets 3.5 mg/kg and placebo on clinical and MRI endpoints and in attainment of No Evidence of Disease Activity (NEDA) in patients with baseline EDSS scores of ≥3.5 or ≤3.0 in CLARITY

## METHODS

- Week 96 data from CLARITY[5] were retrospectively examined across patients with baseline EDSS ≥3.5 or ≤3.0. The current analysis focuses on cladribine tablets 3.5 mg/kg versus placebo, as 3.5 mg/kg is the only approved dose
- Endpoints assessed in this analysis included ARR, proportion of patients relapse free, risk of 3- or 6-month CDP; proportion of patients with no new T1 gadolinium-enhancing (Gd+) lesions and with no new active T2 lesions; and attainment of NEDA, defined as the absence of relapses, 3- or 6-month CDP, and MRI disease activity
- All analyses (using SAS® software version 9.4 or higher) were performed in the intention-to-treat (ITT) population and presented by treatment groups stratified according to baseline EDSS score (≥3.5 or ≤3.0). P values are nominal

## RESULTS

### Patients

- In the ITT population, 433 patients were assigned to cladribine tablets 3.5 mg/kg (baseline EDSS ≥3.5, N=161; EDSS ≤3.0, N=272) and 437 patients to placebo (baseline EDSS ≥3.5, N=174; EDSS ≤3.0, N=263)
- In general, baseline demographic and disease characteristics were well balanced between treatment groups (**Table 1**)
  - Patients in the EDSS ≥3.5 group had worse disease than patients in the EDSS ≤3.0 subgroup: longer disease duration, more T2 lesions, higher mean T2 lesion volume
  - In the placebo EDSS ≥3.5 subgroup, there were more patients with prior use of DMD
  - In the placebo EDSS ≤3.0 subgroup, there were fewer patients with T1 Gd+ lesions

**Table 1. Demographics and Disease Characteristics of Patients at CLARITY Baseline**

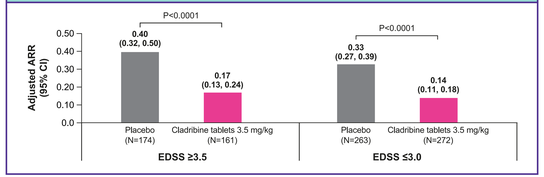
| | EDSS ≥3.5* | | EDSS ≤3.0 | |
|---|---|---|---|---|
| | Placebo (N=174) | Cladribine tablets 3.5 mg/kg (N=161) | Placebo (N=263) | Cladribine tablets 3.5 mg/kg (N=272) |
| **Age (years), mean (SD)** | 41.6 (10.0) | 40.5 (10.3) | 36.8 (9.3) | 36.5 (10.0) |
| **Sex, n (%)** | | | | |
| Male | 58 (33.3) | 56 (34.8) | 91 (34.6) | 79 (29.0) |
| Female | 116 (66.7) | 105 (65.2) | 172 (65.4) | 193 (71.0) |
| **Disease duration (years), mean (SD)** | 6.90 (5.93) | 6.25 (6.74) | 4.05 (4.80) | 3.75 (4.40) |
| **Prior use of DMD, n (%)** | 58 (33.3) | 38 (23.6) | 74 (28.1) | 72 (26.5) |
| **Relapses in prior 12 months, n (%)** | | | | |
| 1 | 119 (68.4) | 111 (68.9) | 187 (71.1) | 192 (70.6) |
| 2 | 47 (27.0) | 41 (25.5) | 63 (24.0) | 64 (23.5) |
| ≥3 | 8 (4.6) | 9 (5.6) | 13 (4.9) | 16 (5.9) |
| **Baseline EDSS score, mean (SD)** | 4.29 (0.68) | 4.17 (0.69) | 2.05 (0.74) | 2.04 (0.72) |
| **Number of T1 Gd+ lesions, mean (SD)** | 0.9 (2.7) | 1.0 (2.5) | 0.7 (1.5) | 1.0 (2.8) |
| **Number of T2 lesions, mean (SD)** | 29.5 (19.1) | 28.3 (17.5) | 25.9 (16.6) | 23.5 (15.3) |
| **T2 lesion volume (cm³), mean (SD)** | 16.3 (12.8) | 19.9 (18.1) | 13.0 (13.2) | 11.9 (14.3) |

*high range of EDSS in this population was 5.5
**DMD**, disease modifying drug; **EDSS**, Expanded Disability Status Scale; **Gd+**, gadolinium enhancing; **SD**, standard deviation

### Annualized Relapse Rate

- More patients treated with cladribine tablets 3.5 mg/kg were relapse free by Week 96 compared with placebo, irrespective of EDSS score at baseline
  - EDSS ≥3.5: 80.1% (cladribine tablets 3.5 mg/kg) vs. 63.2% (placebo)
  - EDSS ≤3.0: 81.6% (cladribine tablets 3.5 mg/kg) vs. 63.1% (placebo)
- Compared with placebo, treatment with cladribine tablets 3.5 mg/kg significantly reduced ARR rate in patients with baseline EDSS ≥3.5 and in patients with baseline EDSS ≤3.0 (both P<0.0001) (**Figure 1**)

**Figure 1. Annualized Relapse Rate at Week 96 of CLARITY According to Baseline EDSS Score**

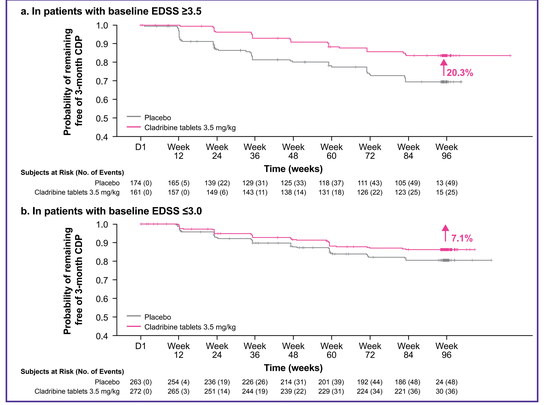



Annualized relapse rate was estimated using a Poisson regression model including effects for treatment group and region and the log of time on study as offset, with P-values determined by the Wald Chi-Square test. **ARR**, annualized relapse rate; **CI**, confidence interval; **EDSS**, Expanded Disability Status Scale

### Time to 3-Month Confirmed Disability Progression

- For patients with baseline EDSS ≥3.5, at Week 96 there was a 20.3% reduction in the risk of 3-month CDP for cladribine tablets 3.5 mg/kg (83.5% [95% confidence interval {CI} 76.6–88.6]) compared with placebo (69.4% [95% CI: 61.6–76.0]), with notable between-group differences seen by Week 24 (**Figure 2a**)
- In the baseline EDSS ≤3.0 group, at Week 96 there was a more moderate 7.1% reduction in the risk of 3-month CDP for cladribine tablets 3.5 mg/kg (86.3% [95% CI: 81.5–89.9]) compared with placebo (80.6% [95% CI: 75.1–85.0], **Figure 2b**)

**Figure 2. Kaplan-Meier Plots Showing Time to 3-month CDP (ITT Population)**




**CDP**, confirmed disability progression; **EDSS**, Expanded Disability Status Scale; **ITT**, intent to treat

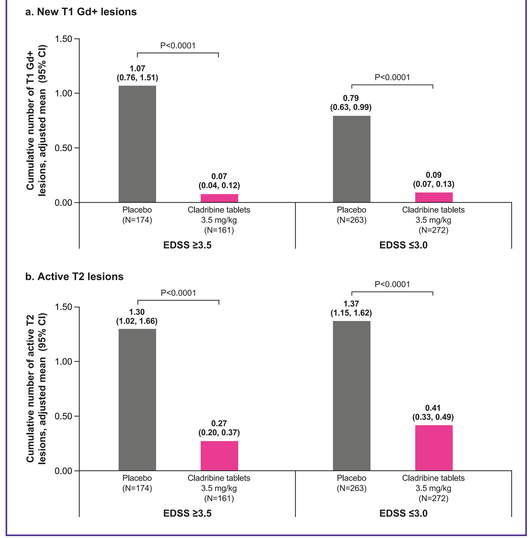
### Time to 6-Month Confirmed Disability Progression

- For patients with baseline EDSS ≥3.5, there was a 12.7% reduction in the risk of 6-month CDP for cladribine tablets 3.5 mg/kg compared with placebo (88.1% vs. 78.2%) at Week 96, with notable between-group differences seen by Week 24 (please see QR code to the right)
- In the baseline EDSS ≤3.0 group, there was a more moderate 5.5% reduction in the risk of 6-month CDP for cladribine tablets 3.5 mg/kg compared with placebo (92.0% vs. 87.2%) at Week 96 (please see QR code to the right)

### MRI Activity

- By Week 96, the risk of new T1 Gd+ lesions was significantly reduced with cladribine tablets 3.5 mg/kg versus placebo regardless of baseline EDSS score (P<0.0001 for each EDSS group) (**Figure 3a**)
- Similarly, the risk of active T2 lesions was significantly reduced at Week 96 with cladribine tablets 3.5 mg/kg compared with placebo (P<0.0001 for each EDSS group) (**Figure 3b**)

**Figure 3. Cumulative Number of Lesions by Week 96 of CLARITY According to EDSS Score at Baseline**




Relative risk and 95% CI were estimated using a Negative Binomial regression model with fixed effect for treatment group, region and number of T1 or T2 lesions at baseline, and with the log of number of scan as the offset; P values were based on the Wald Chi-square test. **CI**, confidence interval; **EDSS**, Expanded Disability Status Scale; **Gd+**, gadolinium enhancing

### No Evidence of Disease Activity (NEDA)

- A greater proportion of patients treated with cladribine tablets 3.5 mg/kg versus placebo achieved NEDA status, irrespective of the baseline EDSS group (**Table 2**)
- Odds ratios (OR) for likelihood of achieving NEDA status favored cladribine tablets 3.5 mg/kg compared with placebo based on 3- and 6-month CDP in the baseline EDSS ≥3.5 group and in the baseline EDSS ≤3.0 group (**Table 2**)

**Table 2. NEDA Status Based on either 3-month or 6-month CDP by Week 96 of CLARITY According to EDSS Score at Baseline**

| | EDSS ≥3.5 | | EDSS ≤3.0 | |
|---|---|---|---|---|
| | Placebo (N=174) | Cladribine tablets 3.5 mg/kg (N=161) | Placebo (N=263) | Cladribine tablets 3.5 mg/kg (N=272) |
| **NEDA (using 3-month CDP)** | | | | |
| Achieved,[a] n (%) | 26 (14.9) | 71 (44.1) | 35 (13.3) | 106 (39.0) |
| Failed,[b] n (%) | 137 (78.7) | 82 (50.9) | 218 (82.9) | 158 (58.1) |
| Unknown,[c] n (%) | 11 (6.3) | 8 (5.0) | 10 (3.8) | 8 (2.9) |
| OR (95% CI) | | 4.40 (2.59, 7.47) | | 4.23 (2.74, 6.54) |
| P value | | <0.0001 | | <0.0001 |
| **NEDA (using 6-month CDP)[d]** | | | | |
| Achieved,[a] n (%) | 28 (16.1) | 71 (44.1) | 35 (13.3) | 112 (41.2) |
| Failed,[b] n (%) | 134 (77.0) | 80 (49.7) | 218 (82.9) | 152 (55.9) |
| Unknown,[c] n (%) | 12 (6.9) | 10 (6.2) | 10 (3.8) | 8 (2.9) |
| OR (95% CI) | | 4.11 (2.44, 6.93) | | 4.62 (3.00, 7.13) |
| P value | | <0.0001 | | <0.0001 |

[a]Patients with no disease activity on all four components; [b]Patients with disease activity on ≥1 component; [c]Patients who withdrew early (<587 days) while meeting NEDA status criteria and patients with missing ≥1 component but meeting NEDA criteria on all others were classified as unknown and excluded from the inferential statistical analysis; [d]Sensitivity analysis. **CDP**, confirmed disability progression; **CI**, confidence interval; **EDSS**, Expanded Disability Status Scale; **NEDA**, No Evidence of Disease Activity; **OR**, odds ratio

## CONCLUSIONS

- **In this *post hoc* analysis of the 96-week CLARITY study, treatment with cladribine tablets 3.5 mg/kg resulted in similar improvements in relapse and MRI outcomes in patients with RRMS regardless of baseline EDSS score**
- **These results are consistent with prior *post hoc* analyses of CLARITY that examined outcomes (relapse and NEDA) by baseline EDSS score[6,7]**

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## ACKNOWLEGMENTS

This study was sponsored by EMD Serono, Inc., a business of Merck KGaA, Darmstadt, Germany (in the US), and Merck Serono SA, Geneva, an affiliate of Merck KGaA, Darmstadt, Germany (ROW). Writing and editorial support for the preparation of this poster was provided by Ying Jean, PhD and Nick White of Ashfield Healthcare Communications (New York, NY, US); funding was provided by EMD Serono. EMD Serono reviewed and provided feedback on the poster. The authors had full control of the poster, and provided their final approval of all content.

## DISCLOSURES

**GC** has received, in the past 24 months, consulting and speaking fees from Novartis, Teva Pharmaceutical Industries Ltd., Teva Italia Srl, Sanofi Genzyme, Genzyme Corporation, Genzyme Europe, Merck KGaA, Merck Serono SpA, Celgene Group, Biogen Idec, Biogen Italia Srl, F. Hoffman-La Roche, Roche SpA, Almirall SpA, Forward Pharma, Medday, Excemed. **GP** has received speaker honoraria and/or consulting fees from Alexion, Biogen Idec, Celgene, EMD Serono, Novartis, Roche/Genentech, Sanofi-Genzyme; and has received research support (to the institution) from Abbvie, Adamas, Alkermes, Biogen Idec, EMD Serono, Roche/Genentech, Sanofi Genzyme, Novartis, and Teva. **FD** and **JA** are employees of EMD Serono, Inc., Billerica, MA, US; a business of Merck KGaA, Darmstadt, Germany. **CL** is an employee of EMD Serono, Inc. Mississauga, ON, CAN; a business of Merck KGaA, Darmstadt, Germany. **KR** has received honoraria for lectures and steering committee meetings from EMD Serono, Biogen, Sanofi-Aventis, Genzyme, Novartis, Teva Neurosciences, Acorda, and Roche/Genentech. SC has received honoraria for lectures/ consultations from Merck, Bayer HealthCare, Sanofi-Aventis, Neurology Reviews, Biogen, Teva Pharmaceuticals, and Actinobac Biomed Inc.; has served on advisory boards for Bayer HealthCare, Merck, Actinobac Biomed, Teva Pharmaceuticals, and Biogen; and received grant support from Bayer HealthCare.

The CLARITY study: NCT00213135



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Presented at ACTRIMS 2020; February 27–29, West Palm Beach, Florida, US