Poster No. 45

CLARITY: An Analysis of Severity and Frequency of Relapses in Patients with Relapsing-Remitting Multiple Sclerosis Treated with Cladribine Tablets or Placebo

S. Schippling[1], M.P. Sormani[2], N. De Stefano[3], G. Giovannoni[4], A. Galazka[5], B. Keller[6], N. Alexandri[6]

[1]University Hospital Zürich, Rämistrasse, Zürich, Switzerland; [2]Department of Health Sciences, University of Genoa and Ospedale Policlinico San Martino IRCCS, Genoa, Italy; [3]Department of Neurological and Behavioural Sciences, University of Siena, Siena, Italy; [4]Queen Mary University of London, Blizard Institute, Barts and The London School of Medicine and Dentistry, London, UK; [5]Merck, Aubonne, Switzerland, a division of Merck KGaA, Darmstadt, Germany; [6]Merck KGaA, Darmstadt, Germany.

INTRODUCTION

- In the CLARITY study, treatment with Cladribine Tablets 10 mg (3.5 mg/kg cumulative dose over 2 years; referred to as Cladribine Tablets 3.5 mg/kg) showed significant efficacy compared with placebo over 2 years in a large cohort of patients with relapsing-remitting multiple sclerosis.[1]
- The annualised qualifying relapse rate at 96 weeks was significantly reduced in the Cladribine Tablets 3.5 mg/kg group compared with placebo (relative reduction of 58%, $P < 0.001$).[1]
- The proportion of patients who remained qualifying relapse-free at 96 weeks was significantly higher in the Cladribine Tablets 3.5 mg/kg group compared with placebo (80% versus 61%, $P < 0.001$).[1]
- Time to first qualifying relapse was significantly longer in the Cladribine Tablets 3.5 mg/kg group compared with the placebo group (hazard ratio: 0.44, $P < 0.001$).[1]

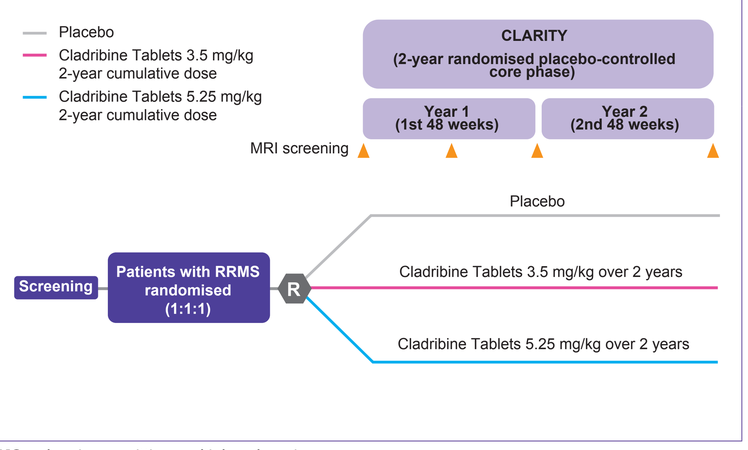
OBJECTIVES

- *Post hoc* evaluation of the effect of Cladribine Tablets 3.5 mg/kg on the rate and severity of relapses (qualifying and all relapses) in the CLARITY study (using hospitalisation and steroid use as proxy indicators), and the effect of adjusting for covariates.
- The aim of this analysis was to compare the effect of Cladribine Tablets versus placebo on qualifying versus to and all relapses.

METHODS

- Qualifying relapse was defined by the Kurtzke Functional Score status and specified clinical parameters.[1]
- Relative risk of qualifying relapse was estimated between patients treated with Cladribine Tablets 3.5 mg/kg (N = 433) and placebo (N = 437) (**Figure 1**) at Weeks 24, 48 and 96 by Poisson regression.
  - Treatment and various alternating covariates were analysed as main effects.
  - Covariates included: gender, age, age at time of diagnosis, disease duration (time since diagnosis), and prior use of disease modifying treatments.

Figure 1. CLARITY Study Design



RRMS, relapsing-remitting multiple sclerosis.

- An analysis of all relapses (including both qualifying and non-qualifying) was also conducted.
- All analyses were *post hoc* and exploratory.

RESULTS

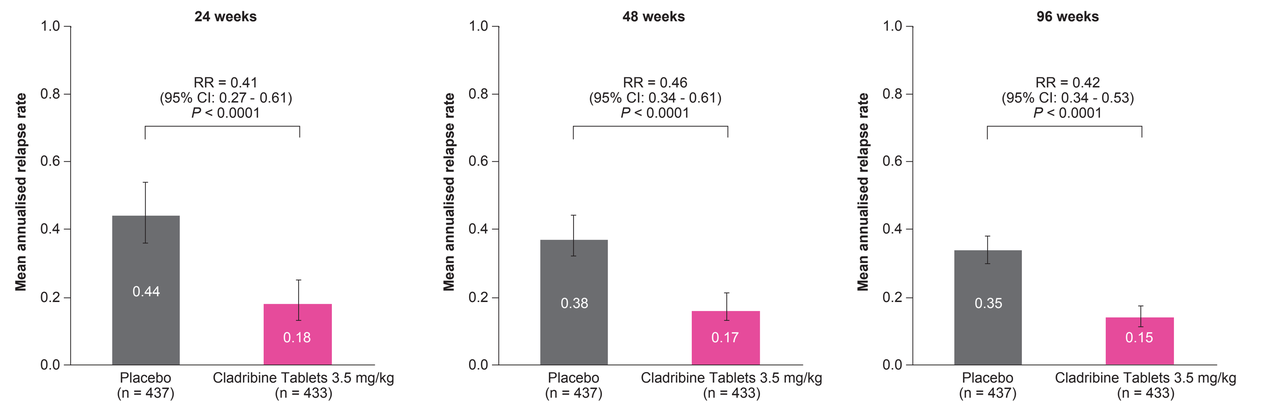
- Baseline demographics and disease characteristics for the placebo and Cladribine Tablets 3.5 mg/kg groups are shown in **Table 1**.
- The number of relapses in the 12 months prior to study were balanced between the treatment groups.

Table 1. Baseline Demographics and Disease Characteristics in CLARITY (Placebo and Cladribine Tablets 3.5 mg/kg Groups Only)

	Placebo (n = 437)	Cladribine Tablets 3.5 mg/kg (n = 433)
Mean age, years	38.7 (9.9)	37.9 (10.3)
Female, n (%)	288 (65.9)	298 (68.8)
Mean disease duration*, years	5.18 (5.45)	4.68 (5.51)
Previous therapy with DMDs, n (%)	132 (30.2)	110 (25.4)
Mean age at time of diagnosis, years	33.6 (9.6)	33.3 (9.7)
Relapses in 12 months prior to study, n (%)		
0	0	0
1	306 (70.0)	302 (69.7)
2	110 (25.2)	106 (24.5)
≥ 3	21 (4.8)	25 (5.8)
Mean EDSS score at baseline	2.94 (1.31)	2.83 (1.25)
Mean number of T1 Gd+ lesions at baseline	0.8 (2.1)	1.0 (2.7)
Mean number of T2 lesions at baseline	27.4 (17.7)	25.3 (16.3)

Data are mean (standard deviation), unless otherwise stated.
*Time since diagnosis.
DMDs, disease modifying drugs; **EDSS**, Expanded Disability Status Scale; **Gd+**, gadolinium-enhancing; **n**, number of patients.

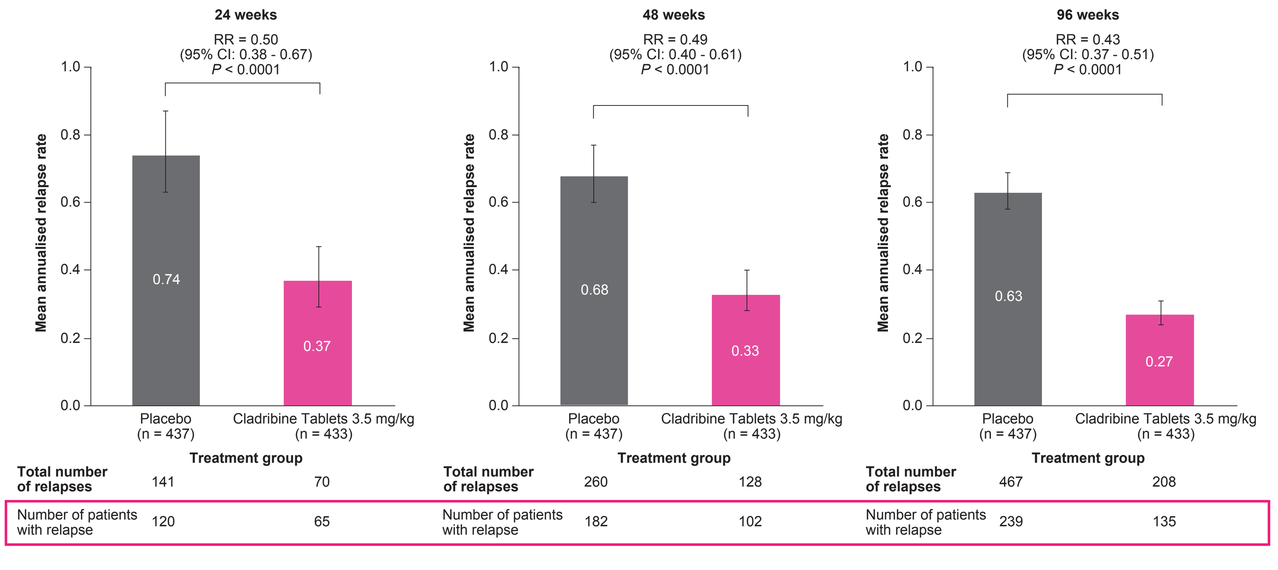
Figure 2. Qualifying Relapse Rates Over Time for Cladribine Tablets 3.5 mg/kg Versus Placebo



	24 weeks		48 weeks		96 weeks	
Total number of relapses	84	34	146	67	258	112
Number of patients with relapse	75	34	111	60	165	85

ARR, annualised relapse rate; **CI**, confidence interval; **RR**, relative risk.
Re-analysis of data since Giovannoni G, et al. *N Engl J Med*. 2010;362:416–426[1]

Figure 3. All Relapse Rates Over Time for Cladribine Tablets 3.5 mg/kg Versus Placebo



	24 weeks		48 weeks		96 weeks	
Total number of relapses	141	70	260	128	467	208
Number of patients with relapse	120	65	182	102	239	135

ARR, annualised relapse rate; **CI**, confidence interval; **RR**, relative risk.

Qualifying relapses

- Compared with placebo, patients in the Cladribine Tablets 3.5 mg/kg group had a significantly ($P < 0.0001$) reduced risk of experiencing a qualifying relapse at Weeks 24, 48 and 96 (**Figure 2**).
- Compared with placebo, patients in the Cladribine Tablets 3.5 mg/kg group had a significantly reduced risk of qualifying relapses leading to hospitalisation and qualifying relapses leading to steroid treatment at all time-points (**Table 2**).
  - At Week 96 annualised relapse rate for Cladribine Tablets 3.5 mg/kg for qualifying relapses leading to hospitalisation was 0.06 (95% CI: 0.05, 0.09) and 0.16 (95% CI: 0.13, 0.19) for placebo.
  - For qualifying relapses requiring steroid treatment it was 0.12 (95% CI: 0.09, 0.14) for Cladribine Tablets 3.5 mg/kg and 0.28 (95% CI: 0.25, 0.32) for placebo.

Table 2. Relative Risk in Qualifying Severe* Relapses Cladribine Tablets 3.5 mg/kg Versus Placebo

Time	Hospitalisation RR (95% CI)	Steroid treatment RR (95% CI)
Week 24	0.43 (0.25, 0.74) $P = 0.0024$	0.40 (0.26, 0.61) $P < 0.0001$
Week 48	0.46 (0.30, 0.70) $P = 0.0004$	0.45 (0.33, 0.62) $P < 0.0001$
Week 96	0.41 (0.29. 0.57) $P < 0.0001$	0.41 (0.32, 0.53) $P < 0.0001$

CI, confidence interval; **RR**, relative risk.
*Resulting in hospitalisation or steroid treatment.

- At Week 96, risk reductions of 59% in qualifying relapses leading to hospitalisation and leading to steroid treatment were observed for patients treated with Cladribine Tablets 3.5 mg/kg versus placebo.
- Wald testing revealed that both age at time of diagnosis ($P = 0.0011$) and prior use of disease modifying drugs ($P = 0.0002$) had a significant effect on ARR.
  - Although significant, neither variable had a large effect (at 96 weeks: unadjusted placebo ARR 0.35 [95% CI: 0.31, 0.39]; adjusted placebo ARR 0.34 [95% CI: 0.30, 0.39]).
- There was no statistically significant effect of either gender ($P = 0.0783$) or disease duration ($P = 0.8770$) on qualifying annualised relapse rate by Week 96.
- None of the covariates influenced the relative risk seen in qualifying relapses for Cladribine Tablets 3.5 mg/kg compared to placebo at Week 96.

All relapses

- Compared with placebo, patients in the Cladribine Tablets 3.5 mg/kg group had a significantly ($P < 0.001$) reduced risk of all relapses at Week 24, 48 and 96 (**Figure 3**).
- A significantly reduced risk of all relapses leading to hospitalisation and all relapses leading to steroid treatment at all time-points was observed in patients in the Cladribine Tablets 3.5 mg/kg group versus placebo (**Table 3**).

Table 3. Relative Risk in All Severe* Relapses Cladribine Tablets 3.5 mg/kg Versus Placebo

Time	Hospitalisation RR (95% CI)	Steroid treatment RR (95% CI)
Week 24	0.44 (0.29, 0.68) $P = 0.0002$	0.43 (0.31, 0.60) $P < 0.0001$
Week 48	0.42 (0.30, 0.59) $P < 0.0001$	0.41 (0.32, 0.53) $P < 0.0001$
Week 96	0.37 (0.29, 0.48) $P < 0.0001$	0.38 (0.31, 0.46) $P < 0.0001$

CI, confidence interval; **RR**, relative risk.
*Resulting in hospitalisation or steroid treatment.

- At Week 96 risk reduction of 63% and 62% in all relapses leading to hospitalisation and leading to steroid treatment, respectively were observed in patients in the Cladribine Tablets 3.5 mg/kg group versus placebo.

CONCLUSIONS

- **The relative risk for qualifying relapses and all relapses was consistently and significantly lower in the Cladribine Tablets 3.5 mg/kg group, relative to placebo, for all time-points (Weeks 24, 48 and 96), including relapses requiring hospitalisation or steroid treatment.**
- **Treatment with Cladribine Tablets 3.5 mg/kg reduced annualised relapses requiring hospitalisation and those requiring steroids by > 50% compared with placebo.**
- **After adjusting for covariates, the treatment benefit of Cladribine Tablets compared with placebo was consistent by any of the model adjustments.**

REFERENCE

1. Giovannoni G, et al. *N Engl J Med*. 2010;362:416–426.

ACKNOWLEDGEMENTS

This study was sponsored by EMD Serono Inc, a business of Merck KGaA, Darmstadt, Germany (in the USA), and Merck Serono SA, Geneva, an affiliate of Merck KGaA Darmstadt, Germany (ROW). Medical writing assistance was provided by Mark O'Connor of inScience Communications, Springer Healthcare, Chester, UK, and was funded by Merck KGaA, Darmstadt, Germany.

DISCLOSURES

SS has been a steering committee member of clinical trials and has received travel support and speaker fees from Almirall, Bayer, Biogen, Sanofi, Merck, Novartis, and TEVA. **MPS** has received consulting fees from Biogen Idec, Merck, Teva, Genzyme, Roche, Novartis, GeNeuro and Medday. **NDS** has received honoraria and consultation fees from Merck Serono S.A., Teva Pharmaceutical Industries, Novartis Pharma AG, Bayer Schering AG, Sanofi-Aventis and Serono Symposia International Foundation. **GG** has received speaker honoraria and consulting fees from Abbvie, Actelion, Almirall, Atara Bio, Bayer Schering Pharma, Biogen Idec, FivePrime, GlaxoSmithKline, GW Pharma, Merck, Pfizer Inc, Protein Discovery Laboratories, Teva Pharmaceutical Industries Ltd, Sanofi-Genzyme, UCB, Vertex Pharmaceuticals, Ironwood, and Novartis; and has received research support unrelated to this study from Biogen Idec, Merck, Novartis, and Ironwood. **AG** is an employee of Merck, Aubonne, Switzerland, a division of Merck KGaA, Darmstadt, Germany. **BK** and **NA** are employees of employee of Merck KGaA, Darmstadt, Germany.

The CLARITY study: NCT00213135

Cladribine Tablets are approved by the European Commission for the treatment of adult patients with highly active relapsing multiple sclerosis (MS) as defined by clinical or imaging features.

GET POSTER PDF

Presented at the European Charcot Foundation (ECF) Congress 2018; 15 - 17 November 2018; Baveno, Italy.