Abstract No. 73

A Pooled Analysis of the Efficacy of Cladribine Tablets 3.5 mg/kg in RMS patients with EDSS ≥ 3.5 or ≤ 3.0 at Baseline in the CLARITY and ONWARD Studies

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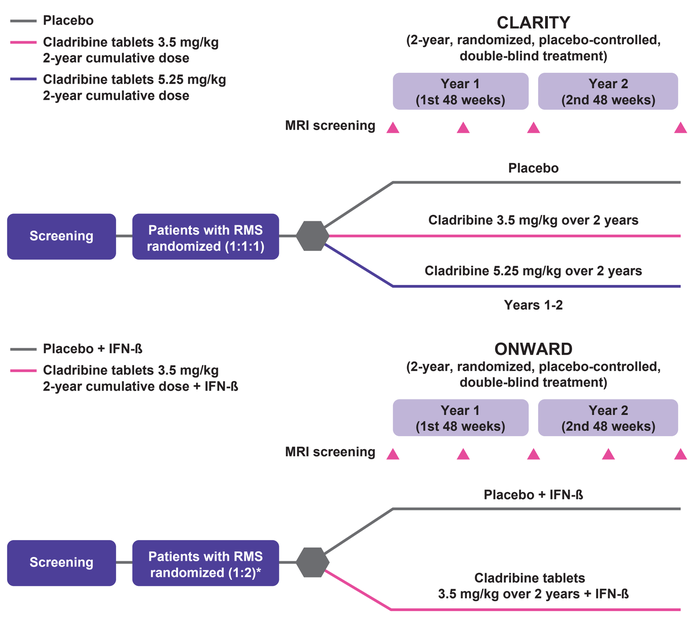
INTRODUCTION

- The CLARITY study evaluated the efficacy of cladribine tablets (3.5 mg/kg and 5.25 mg/kg of bodyweight, cumulative dose) given in short courses annually for 2 years to patients with relapsing multiple sclerosis (RMS; **Figure 1**).[1]
- The ONWARD study evaluated the safety and tolerability of cladribine tablets (3.5 mg/kg and 5.25 mg/kg of bodyweight, cumulative dose) given in short courses annually for 2 years as an add-on to interferon (IFN)-β therapy in patients with RMS who experienced at least one relapse while on IFN-β (**Figure 1**). Treatment with cladribine tablets 5.25 mg/kg was discontinued after an early protocol amendment.[2]

— Efficacy was explored as a secondary objective of the ONWARD study.[2]

Figure 1. CLARITY and ONWARD Study Designs



* Prior to an early protocol amendment, the ONWARD study included randomization to treatment with cladribine tablets 5.25 mg/kg (cumulative dose over 2 years) + IFN-ß.

- Patients with an Expanded Disability Status scale (EDSS) score of ≥ 3.5 are at higher risk of conversion from relapsing-remitting multiple sclerosis (RRMS) to secondary progressive multiple sclerosis (SPMS) with relapses.
- Combining data from the double-blind periods of each study allowed the effects of 2 years' treatment with cladribine tablets (3.5 mg/kg cumulative dose) to be assessed in patients with higher EDSS scores at study entry.

OBJECTIVES

- To assess efficacy of cladribine tablets 3.5 mg/kg in subgroups of patients with EDSS ≥ 3.5 vs. ≤ 3.0 at baseline.

METHODS

- CLARITY and ONWARD were placebo-controlled double-blind studies with a 2-year treatment period.

— In ONWARD all patients received IFN-β plus cladribine tablets or placebo.

- Inclusion criteria are shown in **Table 1.**

Table 1. Inclusion Criteria for CLARITY and ONWARD

Inclusion criteria	CLARITY	ONWARD
Age	18−65 years	18−55 years
MS stage	RRMS	RRMS or relapsing SPMS
DMD use for MS at study entry	Washout of DMDs (for 3 months) prior to study entry was required	Treatment with IFN for ≥ 48 weeks before screening was required
Relapses	≥ 1 relapses within 12 months before study. No relapse within 28 days of screening	≥ 1 relapse while receiving IFN but otherwise clinically stable in the 28 days before screening
EDSS score	0 − ≤ 5.5	1 − ≤ 5.5

DMD, disease modifying drug; **EDSS**, Expanded Disability Status Scale; **IFN**, interferon; **RRMS**, relapsing-remitting multiple sclerosis; **SPMS**, secondary progressive multiple sclerosis.

- Data from the 2-year, double-blind periods of CLARITY and ONWARD were used to analyze the effect of cladribine tablets 3.5 mg/kg (vs. placebo) on annualized relapse rate (ARR) and EDSS progression by comparing patients who entered the study with baseline EDSS ≥ 3.5 and the complementary subgroup with baseline EDSS ≤ 3.0.

Annualized Relapse Rate

- Relative risk (RR) and 95% confidence intervals (CI) were estimated for qualifying ARR in patients treated with cladribine tablets or placebo, using a Poisson regression model with fixed effects for treatment group and study, the number of relapses in previous year as covariate and with the log of time on Study as the offset variable.

— *P* values were based on the Wald Chi-square test.

3- and 6-Month Confirmed Disability Status Scale (EDSS) Progression

- Hazard ratios and 95% CIs for time to 3- or 6-month confirmed EDSS progression with cladribine tablets and placebo were calculated for the intended-to-treat population and for patient subgroups from a Cox proportional hazard model adjusted for study effect and with the EDSS scores at baseline as covariate.
- All analyses were *post hoc* and not pre-specified, no multiplicity adjustments were done to the resulting *P* values. All comparisons where the *P* value was less than 0.05 by statistical testing should be regarded as nominally significant.

RESULTS

- There were a total of 1067 patients who received either placebo (n = 494) or cladribine 3.5 mg/kg (n = 573) in CLARITY and ONWARD (**Table 2**).

— In the placebo group, 292 patients had a baseline EDSS score ≤ 3 and 202 had an EDSS score of ≥ 3.5.

— In the cladribine 3.5 mg/kg arm, there were 361 patients with a baseline EDSS score of ≤ 3 and 212 patients with an EDSS score of ≥ 3.5.

Table 2. Demographics and Baseline Characteristics of Patients Randomized to Placebo or Cladribine Tablets 3.5 mg/kg in the Double-Blind Treatment Periods of CLARITY and ONWARD

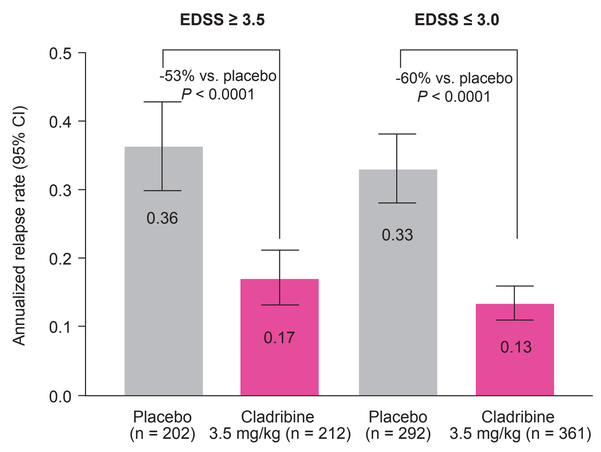
Parameter	Placebo (N = 494)	Cladribine 3.5 mg/kg (N = 573)
Age, years		
mean (SD)	38.9 (9.9)	38.1 (10.3)
median	39.0	38.0
min; max age	18; 64	18; 65
patients aged:		
≤ 40 years, n (%)	277 (56.1)	340 (59.3)
> 40 years, n (%)	217 (43.9)	233 (40.7)
Gender		
males, n (%)	164 (33.2)	181 (31.6)
females, n (%)	330 (66.8)	392 (68.4)
Disease duration, years		
mean (SD)	5.5 (5.6)	5.2 (5.5)
median	3.9	3.5
min; max duration	0.1; 36.3	0.1; 38.1
No prior DMD use, n (%)	305 (61.7)	323 (56.4)
Relapses in prior 12 months categories, n (%)		
0	1 (0.2)	0
1	342 (69.2)	408 (71.2)
2	127 (25.7)	136 (23.7)
≥ 3	24 (4.9)	29 (5.1)
EDSS at baseline		
mean score (SD)	3.0 (1.3)	2.8 (1.2)
median score	3.0	2.5
min; max score	0.0; 5.5	0.0; 6.0
patients with EDSS score:		
≤ 3, n (%)	292 (59.1)	361 (63.0)
≥ 3.5, n (%)	202 (40.9)	212 (37.0)
T1 Gd+ lesions		
mean number (SD)	0.8 (2.2)	1.0 (3.0)
median number	0.0	0.0
min; max number	0; 27	0; 34
patients with no T1 Gd+ lesions, n (%)	350 (70.9)	409 (71.4)
patients with ≥ 1 T1 Gd+ lesion, n (%)	144 (29.1)	164 (28.6)
T2 lesions		
mean number (SD)	28.0 (18.1)	27.3 (18.3)
median number	24.5	23.0
min; max number	2; 134	2; 110
patients with < 9 T2 lesions, n (%)	50 (10.1)	61 (10.6)
patients with ≥ 9 T2 lesions, n (%)	444 (89.9)	512 (89.4)

DMD, disease modifying drug; **EDSS**, Expanded Disability Status Scale; **Gd+**, Gadolinium-enhancing; **SD**, standard deviation.

Relapses

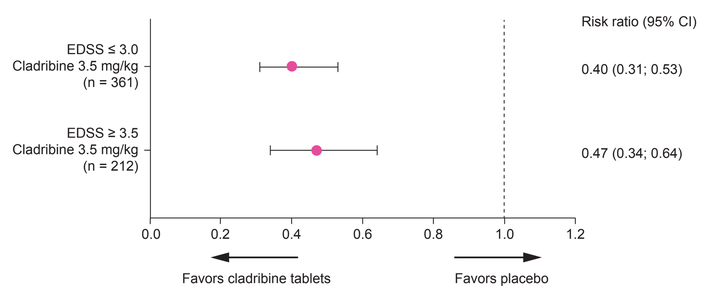
- The observed ARR (95% CI) in the baseline EDSS ≥ 3.5 subgroup was 0.17 (0.13-0.21) for cladribine tablets vs. 0.36 (0.30-0.43) for placebo (**Figure 2**).
- In the baseline EDSS ≤ 3.0 subgroup, ARR (95% CI) was 0.13 (0.11-0.16) for cladribine tablets vs. 0.33 (0.28-0.38) for placebo (**Figure 2**).
- The treatment effect was nominally significant in both EDSS subgroups (**Figure 2**).
- The treatment effect of cladribine 3.5 mg/kg vs. placebo was similar between EDSS subgroups (group by treatment interaction, *P* > 0.05) (**Figure 3**).

Figure 2. Mean Annualized Relapse Rates at 96 Weeks



CI, confidence interval; **EDSS**, Expanded Disability Status Scale.

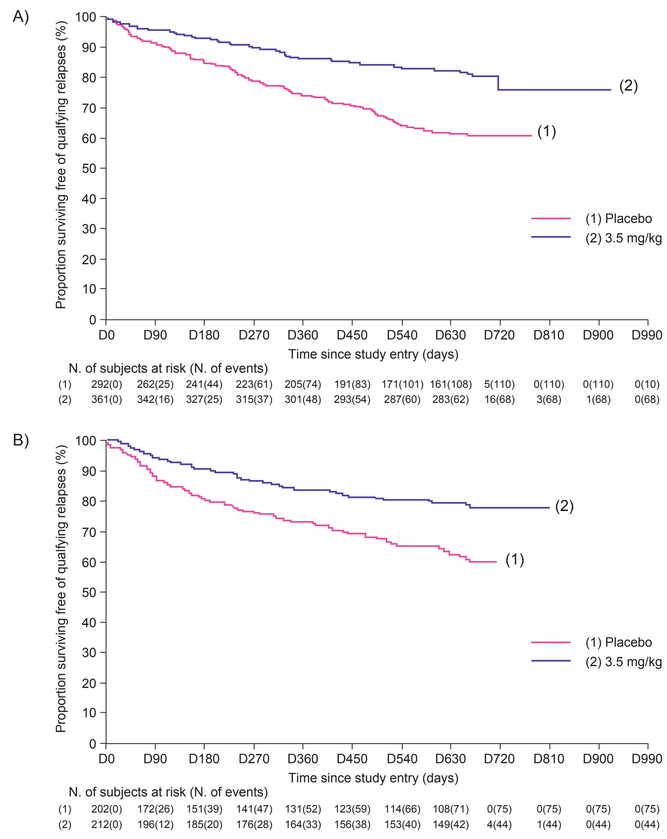
Figure 3. Annualized Qualifying Relapse Risk Ratio



CI, confidence interval; **EDSS**, Expanded Disability Status Scale.

- Compared to placebo, time to first qualifying relapse was significantly longer with cladribine tablets for both high (≥ 3.5) and low (≤ 3.0) EDSS subgroups.
- No significant differences in time to first qualifying relapse were seen between EDSS subgroups ≤ 3.0 vs. ≥ 3.5; **Figures 4 & 5**).

Figure 4. Time to First Qualifying Relapse for the EDSS Baseline ≤ 3.0 subgroup (A) and ≥ 3.5 subgroup (B)

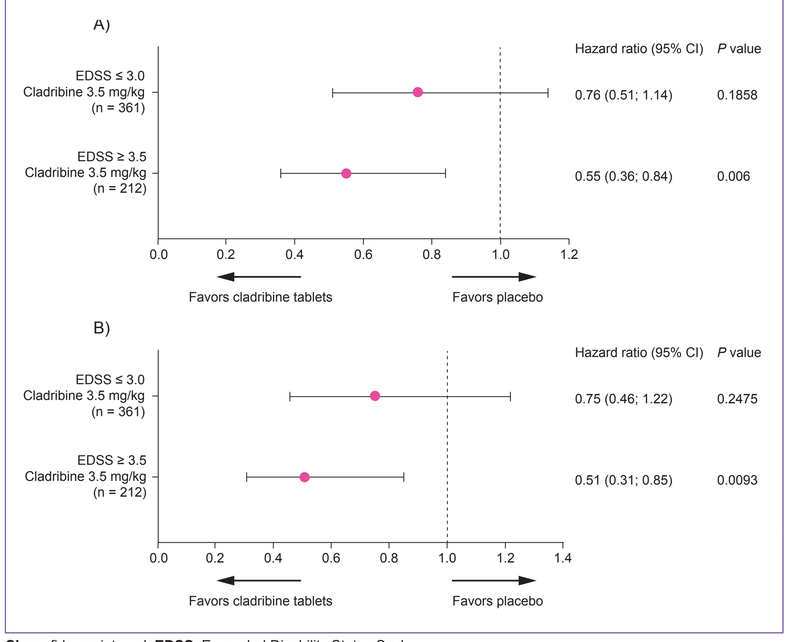


EDSS, Expanded Disability Status Scale.

3- and 6-Month Confirmed Disability Status Scale (EDSS) Progression

- For the EDSS ≥ 3.5 subgroup, time to 3-month and 6-month confirmed EDSS progression was significantly prolonged with cladribine tablets 3.5 mg/kg compared to placebo (data not shown).
- For the EDDS ≥ 3.5 subgroup the risk of 3- and 6-month disability progression was significantly reduced with cladribine tablets compared to placebo (hazard ratio [HR] 0.55, 95% CI 0.36–0.84 and HR 0.51, 95% CI 0.31–0.85; respectively; **Figure 5**).

Figure 5. Effects of Cladribine Tablets 3.5 mg/kg vs. Placebo on Hazard Ratio for Time to A) 3-Month and B) 6-Month Confirmed EDSS Progression in EDSS Subgroups



CI, confidence interval; **EDSS**, Expanded Disability Status Scale.

CONCLUSIONS

- **There was no meaningful difference in the observed treatment effect on ARR between EDSS subgroups supporting the concept that cladribine tablets 3.5 mg/kg is effective for patients with RMS, including those with higher EDSS scores who are at increased risk of conversion to SPMS with relapses.**

REFERENCES

1. Giovannoni G, et al. *N Engl J Med.* 2010;362:416-26.
2. Montalban X, et al. *Neurology*. 2013;80:P07-9 [Abstract]

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DISCLOSURES

GG has received speaker honoraria and consulting fees from Abbvie, Atara Bio, Almirall, 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. **XM** has been a steering committee member of clinical trials or participated in advisory boards of clinical trials with Actelion, Bayer, Biogen, Celgene, Genzyme, Merck, Novartis, Oryzon, Roche, Sanofi-Genzyme and Teva Pharmaceutical **CH** is an employee of Merck KGaA, Darmstadt, Germany. **FD** is an employee of EMD Serono, Inc., a business of Merck KGaA, Darmstadt, Germany.

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