Poster No. DX31

Benefits of cladribine tablets on no evidence of disease activity (NEDA) status in patients with multiple sclerosis: analysis of pooled data from CLARITY and ONWARD

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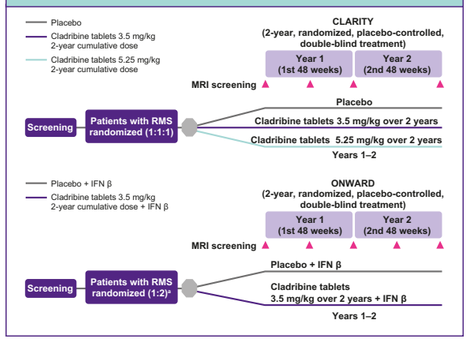
INTRODUCTION

- The CLARITY study evaluated the efficacy of cladribine tablets (3.5 mg/kg and 5.25 mg/kg of body weight, 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 body weight, 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



IFN, interferon; **MRI**, magnetic resonance imaging; **RMS**, relapsing multiple sclerosis.
[a]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 β.

- Previous *post hoc* analyses of CLARITY data have analyzed individual and composite measures of patients with no evidence of disease activity (NEDA).[3]
- Combining efficacy data from the double-blind periods of the CLARITY and ONWARD studies allowed the effects of 2 years' treatment with cladribine tablets on the proportion of patients meeting criteria for NEDA to be assessed.

OBJECTIVE

- To summarize proportions of patients with RMS treated with cladribine tablets achieving NEDA status in the CLARITY and ONWARD studies, including patient subgroups.

METHODS

- Inclusion criteria for each study are shown in **Table 1**.
- 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.

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 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 relapse 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 to ≤5.5	1 to ≤5.5

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

- In CLARITY, magnetic resonance imaging (MRI) scans were carried out at the pre-trial assessment and at Weeks 24, 48, and 96 (or early termination). In ONWARD, MRI scans were carried out at Study Day 1 and Weeks 24, 48, 72, and 96 (or early termination).
- Data from the 2-year, double-blind periods of the CLARITY and ONWARD studies were used to compare the efficacy of cladribine tablets versus placebo in patients with RMS in the intent-to-treat (ITT) population (all patients randomly allocated to cladribine tablets or placebo) and in subgroups defined by baseline characteristics.
- This *post hoc* pooled analysis includes 17 patients who received cladribine tablets 5.25 mg/kg under the original ONWARD protocol.
- Further outcomes from this pooled analysis are described in other presentations at this meeting (posters DX32 and DX33).

NEDA

- NEDA was defined as no qualifying relapses, no 3-month confirmed Expanded Disability Status Scale (EDSS) progression, no new T1 gadolinium-enhancing (Gd+) lesions, and no active T2 lesions.
  - The composite analysis looked at patients who achieved all components of NEDA over the full time periods in CLARITY and ONWARD, and received treatment with cladribine tablets 3.5 mg/kg, 5.25 mg/kg, or placebo. Patients who were missing data for one or more components of NEDA were reported as unknown. Patients who withdrew early (<83 weeks) with no disease activity were reported as unknown.
  - Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for NEDA in patients treated with cladribine tablets 3.5 mg/kg, 5.25 mg/kg, or placebo, in the ITT population and in patient subgroups, from a logistic regression with treatment as fixed effect and study as covariate.

Subgroup analyses

- Endpoints:
  - patients qualifying relapse-free
  - patients free from (1) 3-month confirmed EDSS progression; (2) new T1 Gd+ lesions; (3) active T2 lesions.
- Subgroups:
  - patients with no relapses or ≥1 relapse in the previous year
  - patients with no T1 Gd+ lesions or ≥1 T1 Gd+ lesion at baseline
  - patients with <9 or ≥9 T2 lesions at baseline
  - patients with no prior use of disease-modifying drugs (DMDs) or prior use of DMDs before baseline
  - males or females
  - patients aged ≤40 or >40 years
  - patients with EDSS score ≤3.0 or EDSS score ≥3.5 at baseline
  - patients with or without high disease activity (HDA) at baseline. HDA was defined as patients with ≥2 relapses in the previous year (regardless of previous treatment status), or patients with ≥1 relapse in the previous year while on DMD therapy and ≥1 T1 Gd+ lesion or 9 T2 lesions. This was selected as a representative definition of HDA as there is no consensus on this measure at present.

RESULTS

Patients

- There were 1540 patients in total (**Table 2**; placebo, n=494; cladribine tablets 3.5 mg/kg, n=573; cladribine tablets 5.25 mg/kg, n=473).

Patients achieving NEDA status

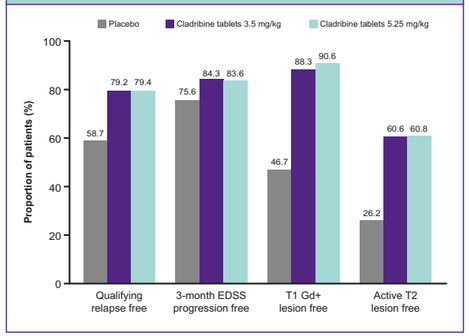
- For each component of NEDA (patients qualifying relapse free, 3-month confirmed EDSS progression-free, T1 Gd+ lesion-free, and active T2 lesion-free), the proportion of patients with NEDA was higher with cladribine tablets 3.5 or 5.25 mg/kg than placebo (**Figure 2**); this trend being especially noticeable for MRI outcomes.
  - Approximately 90% of patients in the two groups treated with cladribine tablets were free from T1 Gd+ lesions versus 47% of placebo-treated patients, and approximately 60% of patients treated with cladribine tablets were free from active T2 lesions compared with 26% of placebo-treated patients.
- Analysis of the composite NEDA measure showed that the odds of remaining free from evidence of disease activity were significantly higher with cladribine tablets 3.5 and 5.25 mg/kg than placebo (p<0.0001 for each, **Table 3**).

Table 2. Demographics and baseline characteristics of patients randomized to placebo or cladribine tablets 3.5 or 5.25 mg/kg in the double-blind treatment periods of CLARITY and ONWARD

Parameter	Placebo (n=494)	Cladribine tablets 3.5 mg/kg (n=573)	Cladribine tablets 5.25 mg/kg (n=473)
Age, years			
Mean (SD)	38.9 (9.9)	38.1 (10.3)	39.1 (9.9)
Median	39.0	38.0	40.0
Min; max	18; 64	18; 65	18; 65
Patients aged:			
≤40 years, n (%)	277 (56.1)	340 (59.3)	253 (53.5)
>40 years, n (%)	217 (43.9)	233 (40.7)	220 (46.5)
Sex			
Male, n (%)	164 (33.2)	181 (31.6)	148 (31.3)
Female, n (%)	330 (66.8)	392 (68.4)	325 (68.7)
Disease duration, years			
Mean (SD)	5.5 (5.6)	5.2 (5.5)	5.1 (5.2)
Median	3.9	3.5	3.5
Min; max	0.1; 36.3	0.1; 38.1	0.0; 31.8
No prior DMD use, n (%)	305 (61.7)	323 (56.4)	320 (67.7)
Relapses in prior 12 months categories, n (%)			
0	1 (0.2)	0	2 (0.4)
1	342 (69.2)	408 (71.2)	334 (70.6)
2	127 (25.7)	136 (23.7)	118 (24.9)
≥3	24 (4.9)	29 (5.1)	19 (4.0)
EDSS score at baseline			
Mean (SD)	3.0 (1.3)	2.8 (1.2)	3.0 (1.4)
Median	3.0	2.5	3.0
Min; max	0.0; 5.5	0.0; 6.0	0.0; 5.5
Patients with EDSS score:			
≤3, n (%)	292 (59.1)	361 (63.0)	260 (55.0)
≥3.5, n (%)	202 (40.9)	212 (37.0)	213 (45.0)
T1 Gd+ lesions			
Mean number (SD)	0.8 (2.2)	1.0 (3.0)	0.9 (2.2)
Median number	0.0	0.0	0.0
Min; max number	0; 27	0; 34	0; 20
Patients with no T1 Gd+ lesions, n (%)	350 (70.9)	409 (71.4)	324 (68.5)
Patients with ≥1 T1 Gd+ lesion, n (%)	144 (29.1)	164 (28.6)	149 (31.5)
T2 lesions			
Mean number (SD)	28.0 (18.1)	27.3 (18.3)	27.8 (16.7)
Median number	24.5	23.0	25.0
Min; max number	2; 134	2; 110	2; 134
Patients with <9 T2 lesions, n (%)	50 (10.1)	61 (10.6)	39 (8.2)
Patients with ≥9 T2 lesions, n (%)	444 (89.9)	512 (89.4)	434 (91.8)

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

Figure 2. Effects of placebo and cladribine tablets 3.5 and 5.25 mg/kg on the proportion of patients free from evidence of disease activity in the individual components of NEDA, excluding unknowns



EDSS, Expanded Disability Status Scale; **Gd+**, gadolinium-enhancing; **NEDA**, no evidence of disease activity.

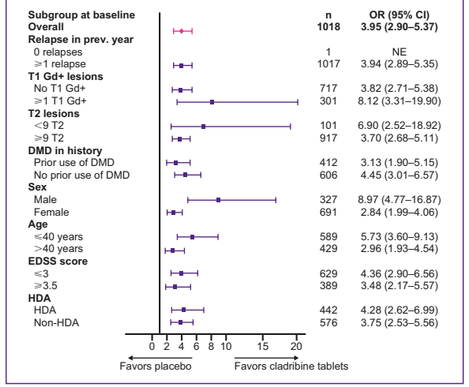
Table 3. Odds ratios for NEDA with placebo and cladribine tablets 3.5 and 5.25 mg/kg in the ITT population in CLARITY and ONWARD

NEDA – composite score, ITT population			
	Placebo (n=494)	Cladribine tablets 3.5 mg/kg (n=573)	Cladribine tablets 5.25 mg/kg (n=473)
Disease activity-free (excluding unknowns), n	469	549	445
Not active (%)	71 (15.1)	229 (41.7)	194 (43.6)
95% CI	12.2–18.7	37.7–45.9	39.1–48.2
Odds ratio		3.95	4.38
95% CI		2.90–5.37	3.19–6.01
p value		<0.0001	<0.0001

CI, confidence interval; **NEDA**, no evidence of disease activity; **ITT**, intention to treat.

- Consistent findings were seen in the subgroups analyzed, including patients with or without evidence of HDA.
  - For each subgroup, the proportion of patients without evidence of disease activity was higher in those who received cladribine tablets 3.5 mg/kg than placebo, and comparison of the composite NEDA score showed that the odds of remaining disease activity-free was significantly higher with cladribine tablets than placebo (p<0.001 for each comparison, **Figure 3**).
  - The only exception was the subgroup of patients with no relapses in the previous year (patient numbers too low for analysis).
  - Similar results were seen in subgroups of patients treated with cladribine tablets 5.25 mg/kg (data not shown).

Figure 3. Effects of cladribine tablets 3.5 mg/kg versus placebo on the odds ratio for composite NEDA score in patient subgroups



CI, confidence interval; **DMD**, disease-modifying drug; **EDSS**, Expanded Disability Status Scale; **Gd+**, gadolinium-enhancing; **HDA**, high disease activity (≥2 relapses in previous year regardless of treatment status, or ≥1 relapse in the previous year while on DMD therapy and ≥1 T1 Gd+ lesion or 9 T2 lesions); **NE**, not estimable; **NEDA**, no evidence of disease activity; **OR**, odds ratio.

- Sensitivity analyses were conducted to assess the impact of classifying patients with unknown status as meeting the criteria for NEDA, or as not meeting these criteria. An assessment of time to disease activity was also carried out (**Table 4**).
- For the 'best case' analysis (patients with unknown status considered as disease-free) and for the 'worst case' analysis (patients with unknown status considered as not free of disease-activity) comparison of the composite NEDA score showed that the odds of remaining disease activity-free were significantly higher with cladribine tablets 3.5 and 5.25 mg/kg compared with placebo.
- For time to disease activity, hazard ratios showed that the probability of remaining disease activity-free at the end of 2 years of double-blind treatment was significantly greater with cladribine tablets 3.5 and 5.25 mg/kg than placebo (p<0.0001 for each dose).

Table 4. NEDA score sensitivity analysis and time to disease activity

	Placebo (n=494)	Cladribine tablets 3.5 mg/kg (n=573)	Cladribine tablets 5.25 mg/kg (n=473)
Best case disease activity-free, n (%)			
Active	398 (80.6)	320 (55.8)	251 (53.1)
Not active	96 (19.4)	253 (44.2)	222 (46.9)
95% CI	16.2–23.2	40.1–48.2	42.5–51.4
Odds ratio		3.20	3.73
95% CI		2.42–4.24	2.79–4.97
p value		<0.0001	<0.0001
Worst case disease activity-free, n (%)			
Active	423 (85.6)	344 (60.0)	279 (59.0)
Not active	71 (14.4)	229 (40.0)	194 (41.0)
95% CI	11.5–17.8	36.0–44.0	36.7–45.5
Odds ratio		3.93	4.17
95% CI		2.89–5.32	3.05–5.70
p value		<0.0001	<0.0001
Time to disease activity			
Probability of being disease activity free[a] (%)	13.0	40.0	40.2
95% CI	9.3–17.3	35.2–44.7	34.6–45.7
Hazard ratio		2.05	2.36
95% CI		1.76–2.38	2.00–2.77
p value		<0.0001	<0.0001

Best case scenario: patients with unknown status are considered disease free. Worst case scenario: patients with unknown status are considered not disease free.
CI, confidence interval; **NEDA**, no evidence of disease activity.
[a]Kaplan-Meier estimate cumulative probability of the absence of disease activity at the end of the 96-week double blind period (at last event). Odds ratio from a logistic regression with treatment as fixed effect and study as covariate. Hazard ratio is estimated from a cox-proportional hazard model with study effect.

CONCLUSIONS

- **Analysis of pooled data from CLARITY and ONWARD showed that cladribine tablets 3.5 and 5.25 mg/kg significantly increased the proportion of patients with no evidence of clinical disease activity compared with placebo in patients with active RMS.**
  - **These benefits were seen across a range of patient subgroups, including patients with clinical and MRI indications of HDA.**

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DISCLOSURES

GG serves on advisory boards for Merck, Biogen Idec, and Vertex Pharmaceuticals; has received speaker honoraria and consulting fees from Bayer Schering Pharma, FivePrime, GlaxoSmithKline, GW Pharma, Merck, Biogen Idec, Pfizer Inc, Protein Discovery Laboratories, Teva Pharmaceutical Industries Ltd, Sanofi-Aventis, UCB, Vertex Pharmaceuticals, Genzyme Corporation, Ironwood, and Novartis; serves on the Merck speakers bureau; and received research support unrelated to this study from Biogen Idec, Merck, Novartis, and Ironwood. **XM** has received speaker honoraria and travel expenses for scientific meetings, is a steering committee member for, and is an advisory board member of clinical trials for Bayer Schering Pharma, Biogen Idec, EMD Serono, Genentech, Genzyme, Novartis, Roche, Sanofi-Aventis, Teva Pharmaceuticals, and Almirall. **CH** is an employee of Merck KGaA, Darmstadt, Germany. **FD** is an employee of EMD Serono, Inc.,* Billerica, MA, USA.

Cladribine tablets is currently under clinical investigation and has not yet been approved by any regulatory authority. Status: March 2017.

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*A business of Merck KGaA, Darmstadt, Germany.

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