Poster No. DX32

Benefits of cladribine tablets on magnetic resonance imaging (MRI) outcomes in patients with multiple sclerosis: analysis of pooled data from the CLARITY and ONWARD studies

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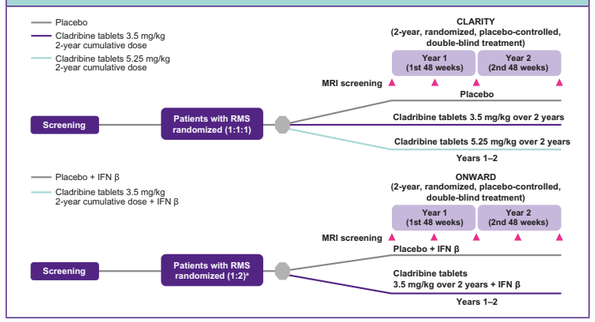
INTRODUCTION

- 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



IFN β, interferon beta; **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

- Treatment with cladribine tablets in CLARITY significantly improved clinical outcomes (relapses and disability progression) vs placebo.[1]
  - Patients in the cladribine tablets 3.5-mg/kg and 5.25-mg/kg groups had fewer lesions per patient per scan than those in the placebo group for gadolinium-enhancing (Gd+) T1 lesions (mean number, 0.12 and 0.11, respectively, vs 0.91 for placebo) and active T2 lesions (mean number, 0.38 and 0.33, respectively, vs 1.43 for placebo).[1]
- Combining efficacy data from the double-blind periods of the CLARITY and ONWARD studies allows the effect of 2 years' treatment with cladribine tablets on magnetic resonance imaging (MRI) outcomes to be assessed.

OBJECTIVE

- To summarize the effects of cladribine tablets on MRI outcomes in the CLARITY and ONWARD studies, including patient subgroups.

METHODS

- Inclusion criteria for each study 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.

- 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.
- In CLARITY, 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 vs 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 DX31 and DX33).

MRI outcomes

- Cumulative new T1 Gd+ lesions and active (new or enlarging) T2 lesions were assessed in the pooled analysis.
- For the ITT population and subgroups, adjusted mean, relative risk (RR) and associated 95% confidence intervals (95% CI) were estimated using a negative binomial regression model corrected for over-dispersion with fixed effects for treatment group and study, with baseline number of T1 Gd+ lesions (or active T2 lesions as appropriate to the analysis) as covariate and with the log of number of scans as the offset variable (p values were based on the Wald Chi-square test).

Subgroup analyses

- Endpoints:
  - cumulative number of new T1 Gd+ lesions
  - cumulative number of 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+ lesions at baseline
  - patients with <9 or ⩾9 T2 lesions at baseline
  - patients with no prior use of 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.

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)
T1 Gd+ lesions			
Mean (SD)	0.8 (2.2)	1.0 (3.0)	0.9 (2.2)
Median	0.0	0.0	0.0
Min; max	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 (SD)	28.0 (18.1)	27.3 (18.3)	27.8 (16.7)
Median	24.5	23.0	25.0
Min; max	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; **Gd+**, gadolinium-enhancing; **SD**, standard deviation.

New T1 Gd+ lesions

- In the ITT population, the mean cumulative number of new T1 Gd+ lesions (**Table 3**) in patients treated with cladribine tablets 3.5 and 5.25 mg/kg represented reductions of 90% or more compared with placebo recipients (RR ratio 0.103, 95% CI 0.076–0.140, p<0.0001; and 0.061, 95% CI 0.043–0.087, p<0.0001, respectively).

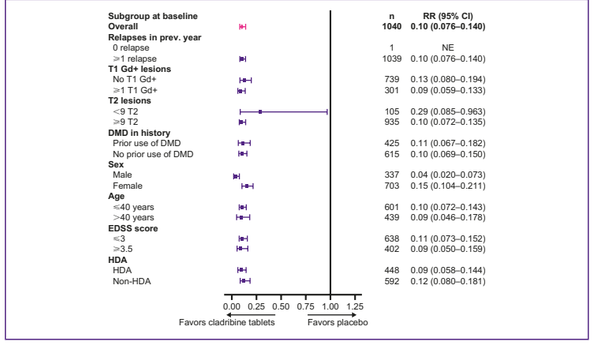
Table 3. RR ratios for mean cumulative numbers of new T1 Gd+ lesions and mean cumulative active T2 lesions in the intent-to-treat population in CLARITY and ONWARD

	Placebo (N=494)	Cladribine tablets 3.5 mg/kg (N=573)	Cladribine tablets 5.25 mg/kg (N=473)
Cumulative number of new T1 Gd+ lesions, ITT population			
N (missing)	481 (13)	559 (14)	459 (14)
Cumulative number of new T1 Gd+ lesions, mean (SD)	2.15 (4.26)	0.25 (0.99)	0.18 (0.77)
Number of scans			
N (missing)	481 (13)	559 (14)	459 (14)
Mean (SD)	2.8 (0.6)	3.0 (0.6)	2.8 (0.5)
Adjusted mean	0.432	0.045	0.026
95% CI	0.334; 0.558	0.034; 0.060	0.018; 0.039
% reduction (cladribine tablets/placebo)		89.7	93.9
95% CI		86.0; 92.4	91.3; 95.7
RR ratio		0.103	0.061
95% CI		0.076; 0.140	0.043; 0.087
P value		<0.0001	<0.0001
Cumulative active new or enlarging T2 lesions, ITT population			
N (missing)	481 (13)	559 (14)	459 (14)
Cumulative number of active T2 lesions, mean (SD)	3.67 (5.35)	1.20 (2.84)	0.84 (1.65)
Number of scans			
N (missing)	481 (13)	559 (14)	459 (14)
Mean (SD)	2.8 (0.6)	3.0 (0.6)	2.8 (0.5)
Adjusted mean	1.243	0.354	0.282
95% CI	1.045; 1.478	0.302; 0.414	0.230; 0.345
% reduction (cladribine tablets/placebo)		71.5	77.3
95% CI		65.1; 76.8	71.9; 81.7
RR ratio		0.285	0.227
95% CI		0.232; 0.349	0.183; 0.281
P value		<0.0001	<0.0001

Adjusted mean, RR, and associated 95% CI were estimated using a negative binomial regression model with fixed effects for treatment group and study, with baseline number of lesions as covariate and with the log of number scans as the offset variable.
CI, confidence interval; **Gd+**, gadolinium-enhancing; **ITT**, intent-to-treat; **RR**, relative risk; **SD**, standard deviation

- Consistent findings were seen in the subgroups, including patients with or without evidence of HDA; each showed a significantly lower RR ratio with cladribine tablets 3.5 mg/kg vs placebo (p<0.0001 for each subgroup except patients with <9 T2 lesions at baseline in which p=0.0434; **Figure 2**). Similar results were seen in subgroups of patients treated with cladribine tablets 5.25 mg/kg (data not shown).

Figure 2. Effects of cladribine tablets 3.5 mg/kg vs placebo on the RR ratio of cumulative new T1 Gd+ lesions in patient subgroups

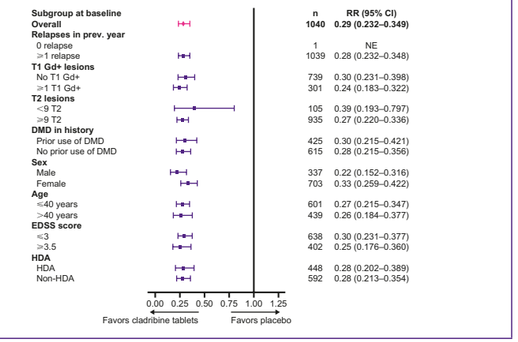


CI, confidence interval; **DMD**, disease-modifying drug; **EDSS**, Expanded Disability Status Scale; **Gd+**, gadolinium-enhancing; **HDA**, high disease activity (⩾2 relapses in previous year regardless of treatment status, or ⩾1 relapse in the previous year while on DMD therapy and ⩾1 T1 Gd+ lesion or 9 T2 lesions); **RR**, relative risk.

Active (new or enlarging) T2 lesions

- In the ITT population, the mean cumulative number of active T2 lesions in patients treated with cladribine tablets 3.5 and 5.25 mg/kg (**Table 3**) represented a 72% and a 77% reduction, respectively compared with placebo recipients (RR ratios 0.285, 95% CI 0.232–0.349, p<0.0001; and 0.227, 95% CI 0.183–0.281, p<0.0001, respectively).
- Consistent findings were seen in the subgroups, including the HDA subgroup: compared with placebo, treatment with cladribine tablets 3.5 mg/kg was associated with a significantly lower RR ratio (p<0.0001 for each subgroup except for patients with <9 T2 lesions at baseline in which p=0.0097) (**Figure 3**). Similar results were also seen in subgroups of patients treated with cladribine tablets 5.25 mg/kg (data not shown).
- The present findings are consistent with previous radiological analyses of the CLARITY study.[3]

Figure 3. Effects of cladribine tablets 3.5 mg/kg vs placebo on the RR ratio of cumulative active T2 lesions 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); **RR**, relative risk.

CONCLUSIONS

- **Analysis of pooled CLARITY and ONWARD data showed that cladribine tablets 3.5 and 5.25 mg/kg significantly reduced the cumulative number of new T1 Gd+ lesions by ~90% and active T2 lesions by ~75% compared with placebo in patients with active RMS.**
  - **These benefits were consistently seen across a range of patient subgroups, including patients with disease (clinical and MRI) and demographic indicators of higher disease activity.**

REFERENCES

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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. **GC** has received consulting fees from Novartis, Teva Pharmaceutical Industries Ltd., Sanofi-Aventis, Merck, and Bayer Schering; lecture fees from Novartis, Teva Pharmaceutical Ind. Ltd., Sanofi-Aventis, Merck Serono, Biogen Dompè, Bayer Schering, and Serono Symposia International Foundation; and trial grant support from Novartis, Teva Pharmaceutical Industries Ltd., Sanofi-Aventis, Merck, Biogen Dompè, and Bayer Schering. **XM** has received speaker honoraria and travel expenses for scientific meetings, steering committee member, and 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: September 2016.

The CLARITY study: NCT00213135, the ONWARD study NCT00436826

*A business of Merck KGaA, Darmstadt, Germany.

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