Poster No. DX30

Durable efficacy of cladribine tablets in patients with multiple sclerosis: analysis of relapse rates and relapse-free patients in the CLARITY and CLARITY extension studies

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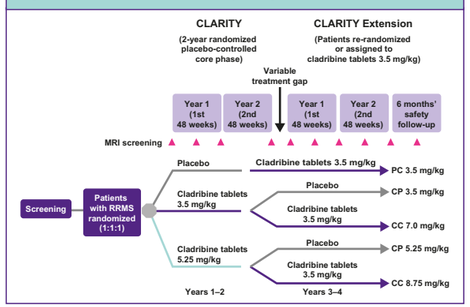
INTRODUCTION

- In the CLARITY study, cladribine tablets, given annually for 2 years in short-duration courses (3.5 mg/kg and 5.25 mg/kg of bodyweight, cumulative dose) significantly improved clinical (relapses and disability progression) and magnetic resonance imaging (MRI) outcomes in patients with relapsing multiple sclerosis.[1]
- The CLARITY Extension (EXT) study compared the safety and efficacy of 2 years' additional cladribine tablet treatment versus no additional treatment and the effect of switching from two courses of placebo to two courses of cladribine tablets (**Figure 1**).

Figure 1. CLARITY Extension study design



MRI, magnetic resonance imaging; **RRMS**, relapsing–remitting multiple sclerosis.

OBJECTIVE

- To assess efficacy outcomes in CLARITY EXT and compare with those obtained in the same patient groups during CLARITY.

METHODS

- Placebo recipients in CLARITY were assigned to cladribine tablets 3.5 mg/kg in CLARITY EXT and all other patients were re-randomized 2:1 to cladribine tablets 3.5 mg/kg or placebo for 2 years (Table 1).

Table 1. Treatment group allocation in CLARITY Extension

		Treatment received in CLARITY Extension	
		Placebo	Cladribine tablets 3.5 mg/kg
Treatment received in CLARITY	Placebo	N/A	PC 3.5 mg/kg
	Cladribine tablets 3.5 mg/kg	CP 3.5 mg/kg	CC 7.0 mg/kg
	Cladribine tablets 5.25 mg/kg	CP 5.25 mg/kg	CC 8.75 mg/kg

N/A, not applicable.

- There was a variable treatment gap between the final CLARITY and first CLARITY EXT visits, with an overall median duration of ~41 weeks.
- After CLARITY EXT, patients entered a 6-month safety follow-up.
- Results are presented for annualized relapse rates (ARRs), proportion of patients who qualified as relapse free, and mean numbers of new T1 gadolinium-enhancing (Gd+) lesions.
- Efficacy objectives are exploratory; all determinations of significance are nominal.

RESULTS

Patients

- 806 patients were randomized/assigned to treatment in CLARITY EXT (**Table 2**).
- The treatment gap between CLARITY and CLARITY EXT varied within each group, but was distributed similarly across groups (**Table 2**).

Table 2. Baseline demographics and disease characteristics in CLARITY Extension

	CP 3.5 mg/kg (n=98)	CP 5.25 mg/kg (n=92)	CC 7 mg/kg (n=186)	CC 8.75 mg/kg (n=186)	PC 3.5 mg/kg (n=244)
Age, years	40.7 (10.7)	40.8 (9.6)	40.6 (10.5)	41.4 (10.1)	41.6 (9.6)
Female, n (%)	67 (68.4)	59 (64.1)	124 (66.7)	125 (67.2)	156 (63.9)
White, n (%)	96 (98.0)	90 (97.8)	181 (97.3)	180 (96.8)	240 (98.4)
Weight, kg	67.93 (14.89)	70.53 (15.16)	68.91 (14.09)	68.56 (14.01)	70.68 (15.56)
DMD use between CLARITY and CLARITY EXT, n (%)	2 (2.0)	0	0	0	4 (1.6)
Relapsed between CLARITY and CLARITY EXT, n (%)	9 (9.2)	8 (8.7)	17 (9.1)	18 (9.7)	46 (18.9)
Disease duration,[a] years	10.1 (6.7)	12.3 (8.0)	10.4 (7.1)	11.9 (7.9)	10.8 (6.8)
Median EDSS score (min; max)	2.5 (0.0; 6.5)	2.5 (0.0; 6.5)	2.5 (0.0; 6.5)	2.5 (0.0; 6.5)	3.0 (0.0; 6.5)
Median gap between studies (min; max), weeks	41.3 (0.1; 116.0)	43.1 (0.3; 112.9)	41.4 (0.4; 115.3)	39.5 (0.9; 111.0)	39.7 (0.3; 118.0)

Data are mean (SD), unless otherwise stated.
[a]Time from first attack.
DMD, disease-modifying drug; **EDSS**, Expanded Disability Status Scale.

ARR

- ARR was significantly lower in CLARITY EXT than CLARITY for patients in the PC 3.5 mg/kg group (0.26 vs 0.10, p<0.0001; **Figure 2**).
- There were no significant differences in ARR in CLARITY and CLARITY EXT in any of the other groups (**Figure 2**).

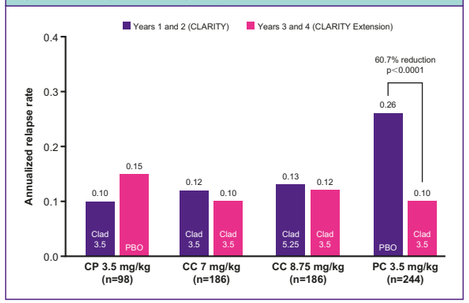
Proportion of patients who qualified as relapse free

- Overall, the proportion of patients who were reported as relapse free was high (>75%) across all groups in CLARITY EXT (**Figure 3**).
- Comparing groups between CLARITY and CLARITY EXT, there were no differences between study phases in the proportions of patients who remained relapse free, except in the PC 3.5 mg/kg group (58.0% vs 79.6%, p<0.0001; **Figure 3**).

Mean numbers of new T1 Gd+ lesions

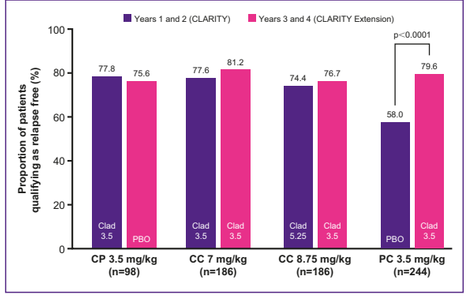
- The mean number of new T1 Gd+ lesions was low in all treatment groups (**Figure 4**), but significant differences were seen between CLARITY and CLARITY EXT for the CP 3.5-, CC 7.0- and PC 3.5-mg/kg groups, but not the CC 8.75-mg/kg group.
- Patients who received placebo in CLARITY (PC 3.5 mg/kg) showed the highest mean number of new T1 Gd+ lesions (0.68).
  - Compared with CLARITY, these patients experienced a 90.4% relative reduction in new T1 Gd+ after receiving cladribine tablets 3.5 mg/kg during CLARITY EXT (0.07, p<0.001).

Figure 2. ARR by treatment group, for CLARITY and CLARITY Extension



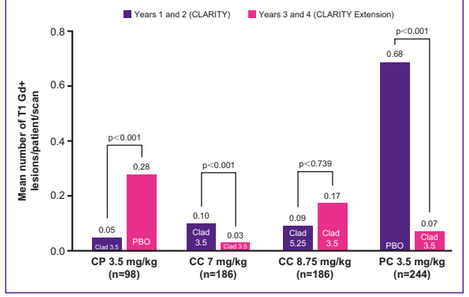
Clad, cladribine tablets; **PBO**, placebo.

Figure 3. Proportion of patients who remained relapse free[a] in CLARITY Extension irrespective of their treatment in CLARITY



Clad, cladribine tablets; **PBO**, placebo.
[a]Denotes qualifying relapses.

Figure 4. Mean per-scan number of new T1 Gd+ lesions in patients in CLARITY Extension



Clad, cladribine tablets; **Gd+**, gadolinium-enhancing; **PBO**, placebo.

- Patients who received cladribine tablets 3.5 mg/kg in CLARITY and 3.5 mg/kg in CLARITY EXT (CC 7 mg/kg) showed a low mean number of new T1 Gd+ lesions during CLARITY (0.10), and a small but significant reduction in CLARITY EXT (0.03, p<0.001).
- Patients who received cladribine tablets 5.25 mg/kg in CLARITY and 3.5 mg/kg in CLARITY EXT (CC 8.75 mg/kg) also showed a low mean number of new T1 Gd+ lesions during CLARITY (0.09) with no significant change during CLARITY EXT.
- Patients who received cladribine tablets 3.5 mg/kg in CLARITY and placebo in CLARITY EXT (CP 3.5 mg/kg) showed a low mean number of T1 Gd+ lesions during CLARITY (0.05) and a significant increase during CLARITY EXT (CP 3.5 mg/kg=0.28, p<0.001).
  - Despite this increase, the value was >2-fold lower than in patients treated with placebo in CLARITY (PC 3.5-mg/kg=0.68)
- Analysis of the distribution of T1 Gd+ lesions showed that the increase in mean T1 Gd+ counts in the CP 3.5-mg/kg group was associated with a subgroup of patients (11.6%) in whom the mean number of new T1 Gd+ lesions was ⩾ 1.0 (**Table 3**).

Table 3. Mean number of T1 Gd+ lesions/patient/scan by category, ITT analysis

	CP 3.5 mg/kg (n=98)	CC 7 mg/kg (n=186)	CC 8.75 mg/kg (n=186)	PC 3.5 mg/kg (n=244)
N (missing)	95 (3)	178 (8)	180 (6)	236 (8)
Mean number of new T1 Gd+ lesions per subject per scan				
<1.0, n (%)	84 (88.4)	178 (100)	175 (97.2)	234 (99.2)
≥1.0, n (%)	11 (11.6)	0 (0.0)	5 (2.9)	2 (0.8)

Gd+, gadolinium-enhancing; **ITT**, intent-to-treat.

Treatment gap between CLARITY and CLARITY EXT

- The mean per-scan number of new T1 Gd+ lesions was also analyzed by gap duration to assess if there was evidence of higher MRI activation in patients with a longer duration since the last dose of cladribine tablets.
  - 10.7% of patients experienced a gap ⩽4 weeks
  - 44.8% had a gap of >4 to ⩽43 weeks
  - 44.5% had a gap of >43 weeks.
- For patients with a gap of ⩽4 weeks, the time since the start of CLARITY was around 4.5 years versus 6.5 years for those who experienced a gap duration >43 weeks.
- In the CP 3.5-mg/kg group, T1 Gd+ MRI activity was greatest in patients who experienced the longest treatment gap.
  - The mean number of new T1 Gd+ lesions was higher among patients with a gap duration >43 weeks (0.39) than among those with a gap duration between 4 and 43 weeks (0.20), or ⩽4 weeks (0.19).
  - This pattern of results was not seen in the CP 5.25-mg/kg group.

CONCLUSIONS

- **Comparing CLARITY versus CLARITY EXT demonstrates the durable clinical benefits of cladribine tablets that persisted even in patients who received cladribine tablets in CLARITY and then placebo in CLARITY EXT.**
- **Patients who received placebo in CLARITY and then switched to cladribine tablets in CLARITY EXT experienced a significantly reduced ARR and increased proportion of relapse-free patients.**
- **In patients who received cladribine tablets in CLARITY, further treatment in CLARITY EXT did not bring additional efficacy.**
- **T1 Gd+ MRI activity was low in the majority of patients in each group at the end of CLARITY EXT, with patients who received placebo in CLARITY and cladribine tablets 3.5 mg/kg in CLARITY EXT experiencing a significant reduction in new T1 Gd+ lesions.**
- **A subgroup of patients who experienced a prolonged treatment gap showed a slight increase in T1 Gd+ activity but this appeared to have no impact on the persistent clinical benefits of cladribine tablets.**

REFERENCES

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

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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 Ind. 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 Ind. 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 Ind. Ltd., Sanofi-Aventis, Merck, Biogen Dompè, and Bayer Schering. **SC** has received honoraria for lectures/consultations from Merck Serono, Bayer HealthCare, Sanofi-Aventis, Neurology Reviews, Biogen Idec, Teva Pharmaceuticals, and Actinobac Biomed Inc.; has served on advisory boards for Bayer HealthCare, Merck, Actinobac Biomed, Teva Pharmaceuticals, and Biogen Idec; and received grant support from Bayer HealthCare. **PR** has received honoraria for lectures/steering committee meetings from Merck, Biogen Idec, Bayer Schering Pharma, Boehringer-Ingelheim, Sanofi-Aventis, Genzyme, Novartis, Teva Pharmaceutical Industries, and Serono Symposia International Foundation. **KR** has received honoraria for lectures and steering committee meetings from EMD Serono, Biogen Idec, Sanofi-Aventis, Genzyme, Novartis, Teva Neurosciences, Acorda and Roche/Genentech. **PS-S** has served on advisory boards for Biogen Idec, Merck, Novartis, Genmab, Teva, Elan, and GSK; on steering committees or independent data monitoring boards in trials sponsored by Merck, Genmab, Teva, GSK, and Bayer Schering; has served as Editor-in-Chief of the European Journal of Neurology, is currently editorial board member for Multiple Sclerosis Journal, European Journal of Neurology, and Therapeutic Advances in Neurological Disorders; has received speaker honoraria from Biogen Idec, Merck Serono, Teva, Bayer Schering, Sanofi-Aventis, Genzyme, and Novartis; and has received payment for writing/reviewing manuscripts from IBI Consulting, a division of Informa plc. His department has received research support from Biogen Idec, Bayer Schering, Merck Serono, Teva, Baxter, Sanofi-Aventis, BioMS, Novartis, Bayer, RoFAR, Roche, Genzyme, the Danish Multiple Sclerosis Society, the Danish Medical Research Council, the European Union Sixth Framework Programme: Life sciences, Genomics and Biotechnology for health. **PV** has received honoraria and consulting fees from Biogen Idec, Sanofi, Bayer, Novartis, Merck, GSK, and Almirall; and research support from Biogen Idec, Sanofi, Bayer, and Merck. **CH** is an employee of Merck KGaA, Darmstadt, Germany. **AKA** and **FD** are employees 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.

The CLARITY study: NCT00213135, the CLARITY EXT study: NCT00641537.

*A business of Merck KGaA, Darmstadt, Germany.

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