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Long-term Disease Stability Assessed by the Expanded Disability Status Scale in Patients Treated with Cladribine Tablets in the CLARITY and CLARITY Extension Studies

G. Giovannoni[1], G. Comi[2], K. Rammohan[3], P. Rieckmann[4], P. Vermersch[5], F. Dangond[6], B. Keller[7], D. Jack[7]

[1]Queen Mary University of London, Blizard Institute, Barts and The London School of Medicine and Dentistry, London, UK; [2]Department of Neurology and Institute of Experimental Neurology, Università Vita-Salute San Raffaele, Ospedale San Raffaele, Milan, Italy; [3]University of Miami School of Medicine, Department of Neurology, MS Research Center, Clinical Research Building, Miami, FL, United States; [4]Department of Neurology, Medical Park Loipl, and University of Erlangen, Erlangen, Germany; [5]Univ. Lille, INSERM U995, CHU Lille, FHU Imminent, Lille, France; [6]EMD Serono Research & Development Institute Inc., Billerica, MA, United States; [7]Merck KGaA, Darmstadt, Germany

INTRODUCTION

- The CLARITY study demonstrated that treatment with cladribine tablets 10 mg (cumulative dose 3.5 mg/kg over 2 years, henceforth referred to as cladribine tablets 3.5 mg/kg [CT3.5]) significantly reduced relapse rates and slowed disability progression versus placebo in relapsing-remitting multiple sclerosis (RRMS) patients.[1]
- Moreover, the CLARITY Extension study concluded that treatment with cladribine tablets for 2 years followed by treatment with placebo for 2 years produced similar clinical benefits to 4 years of cladribine tablets treatment but with lower incidence of grade 3/4 lymphopenia.[2]
- Disease stability in MS can be assessed through the Expanded Disability Status Scale (EDSS). The scale for neurological impairment ranges from 0–10 where a higher score indicates a greater degree of disability and therefore progression of the disease.[1]

OBJECTIVE

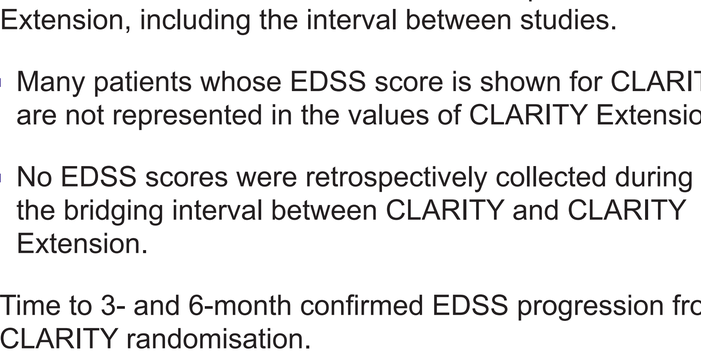
- To evaluate *post hoc,* long-term disease stability assessed by the EDSS score after treatment with CT3.5 in patients with RRMS enrolled in CLARITY and CLARITY Extension.

METHODS

Eligibility and Endpoints

- Patients enrolled into CLARITY Extension who were randomised to CT3.5 in CLARITY with at least one post-baseline EDSS measurement were included for analysis.
  - There was a delay in starting the CLARITY Extension study; after completing CLARITY there was a variable bridging interval (median duration: 43 weeks) between studies where no cladribine tablets were administered.[2]
  - Two treatment groups were investigated (**Figure 1**):
    - CP3.5: CT3.5 in CLARITY followed by placebo in CLARITY Extension.
    - CC7: CT3.5 in CLARITY followed by CT3.5 in CLARITY Extension.
- Endpoints:
  - EDSS scores over time at 6-monthly intervals, from CLARITY randomisation to end of follow-up in CLARITY Extension, including the interval between studies.
    - Many patients whose EDSS score is shown for CLARITY are not represented in the values of CLARITY Extension.
    - No EDSS scores were retrospectively collected during the bridging interval between CLARITY and CLARITY Extension.
  - Time to 3- and 6-month confirmed EDSS progression from CLARITY randomisation.
- EDSS score improvement or worsening each year was defined as any increase or decrease in minimum EDSS score at 6-monthly intervals. All other cases were classified as stable.
- An increase or decrease was defined as EDSS score changes of:
  - At least 1.5 points, if baseline EDSS score = 0.
  - At least 1 point, if baseline EDSS score ≤ 4.5.
  - At least 0.5 points, if baseline EDSS score ≥ 5.

Figure 1. CLARITY/CLARITY Extension Study Arms Under Analysis



The only approved dose of cladribine tablets is 3.5 mg/kg of body weight over 2 years. Following completion of the two treatment courses, no further cladribine treatment is required in Years 3 and 4.

Statistical Analyses

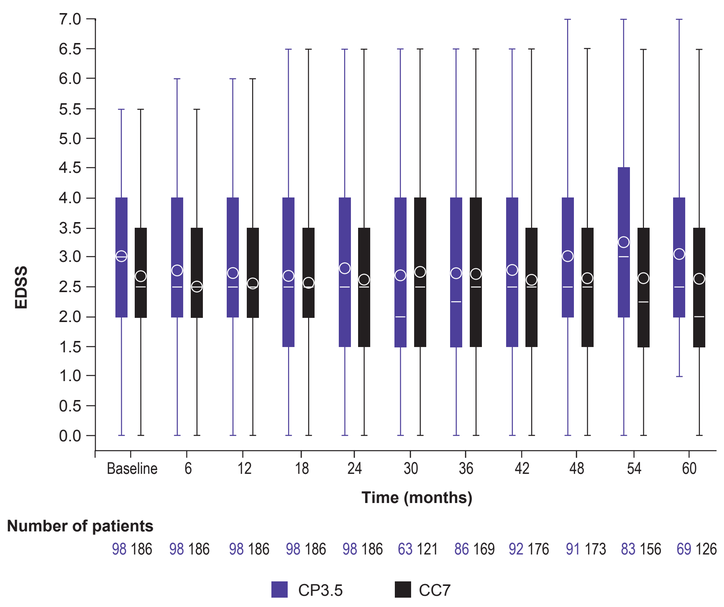
- This was a *post hoc* exploratory analysis of a subset of patients who completed 6 years of follow-up.
- EDSS score over time was descriptively analysed (median, 95% confidence interval [CI]) at 6-monthly intervals, overall and by bridging interval length (≤ 43 weeks versus > 43 weeks).
- Improvement, worsening and stability of EDSS score over 12 months were descriptively analysed (n, %).
- Three- and 6-month EDSS progression from CLARITY entry was analysed by Kaplan-Meier plots.

RESULTS

EDSS Over Time

- Five years after CLARITY baseline, including variable bridging interval, median EDSS score remained stable compared with baseline values for both groups (**Figure 2**).
  - Median EDSS score remained between 2.0–3.0 up to 60 months in the CP3.5 group (n = 69). Median change in EDSS score was 0 points up to 60 months.
  - In the CC7 group (n = 126), median EDSS score ranged between 2.0–2.5 up to 60 months.
- Median (95% CI) EDSS score for patients in the CP3.5 group at 5 years was 2.5 (2.0–3.5) compared with 3.0 (2.5–3.5) at baseline.
- In the CC7 group, median EDSS score (95% CI) was 2.0 (2.0–3.0) compared with 2.5 (2.5–3.0) at baseline.
- Similar results were observed for both groups when split by variable bridging interval of ≤ or > 43 weeks.

Figure 2. EDSS Score Over Time in Patients Treated with CP3.5 and CC7

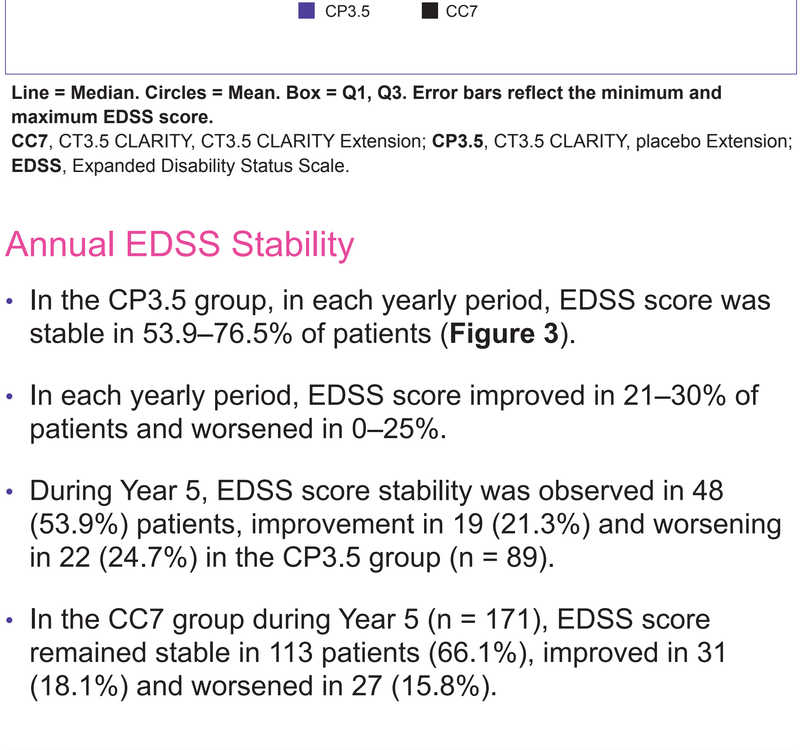


Line = Median. Circles = Mean. Box = Q1, Q3. Error bars reflect the minimum and maximum EDSS score.
CC7, CT3.5 CLARITY, CT3.5 CLARITY Extension; **CP3.5**, CT3.5 CLARITY, placebo Extension; **EDSS**, Expanded Disability Status Scale.

Annual EDSS Stability

- In the CP3.5 group, in each yearly period, EDSS score was stable in 53.9–76.5% of patients (**Figure 3**).
- In each yearly period, EDSS score improved in 21–30% of patients and worsened in 0–25%.
- During Year 5, EDSS score stability was observed in 48 (53.9%) patients, improvement in 19 (21.3%) and worsening in 22 (24.7%) in the CP3.5 group (n = 89).
- In the CC7 group during Year 5 (n = 171), EDSS score remained stable in 113 patients (66.1%), improved in 31 (18.1%) and worsened in 27 (15.8%).

Figure 3. Change in EDSS Score in Each 12 Month Period Up to 5 Years in the CP3.5 and CC7 Patient Groups



Worsened: any increase in EDSS score ≥ 1 (baseline EDSS 0.5–4.5) OR ≥ 1.5 (EDSS 0) OR ≥ 0.5 (EDSS ≥ 5.0).

Improved: any decrease in EDSS score ≥ 1 (baseline EDSS 1–4.5) OR ≥ 0.5 (EDSS ≥ 5.0).

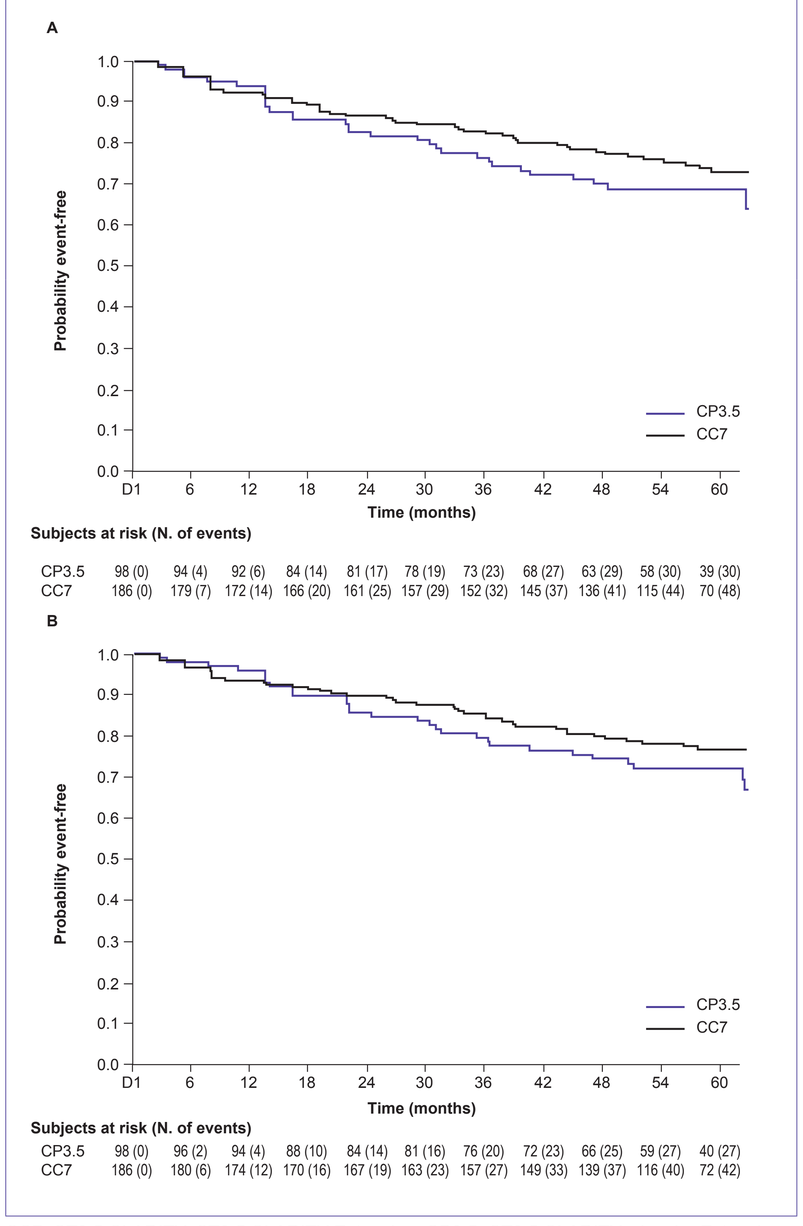
Stable: all remaining cases i.e. increase or decrease < 1.0 (baseline EDSS 0.5–4.5) OR < 1.5 (EDSS 0) OR no change (EDSS ≥ 5.0).

CC7, CT3.5 CLARITY, CT3.5 CLARITY Extension; **CP3.5**, CT3.5 CLARITY, placebo Extension; **EDSS**, Expanded Disability Status Scale.

Time to EDSS Progression

- In both the CP3.5 and CC7 groups, less than 30% of subjects reached 3-month confirmed EDSS progression by 5 years (**Figure 4A**).
- A similar pattern was observed with time to 6-month confirmed EDSS progression. Less than 30% of subjects had confirmed EDSS progression in both the CP3.5 and CC7 groups (**Figure 4B**).

Figure 4. Time to 3- (A) and 6-Month (B) Confirmed EDSS Progression



CC7, CT3.5 CLARITY, CT3.5 CLARITY Extension; **CP3.5**, CT3.5 CLARITY, placebo Extension; **D1**, randomisation date; **EDSS**, Expanded Disability Status Scale.

CONCLUSIONS

- **Median EDSS score remained stable for up to 5 years post-CLARITY baseline in both the CP3.5 and CC7 treatment groups.**
- **Over 50% of patients had stable EDSS score up to 5 years from baseline.**
- **Less than 30% of subjects reached 3- or 6-month confirmed EDSS progression at 5 years.**

REFERENCES

1. Giovannoni G, et al. *N Engl J Med*. 2010;362:416-426.
2. Giovannoni G, et al. *Mult Scler J*. 2018;24:1594-1604.

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DISCLOSURES

GG has received speaker honoraria and consulting fees from Abbvie, Actelion, Atara Bio, Almirall, Bayer Schering Pharma, Biogen Idec, FivePrime, GlaxoSmithKline, GW Pharma, Merck & Co., Merck KGaA, 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 & Co., Novartis, and Ironwood. **GC** has received consulting fees from Novartis, Teva Pharmaceutical Industries Ltd., Sanofi-Aventis, Merck , Receptos, Biogen Idec, Genentech-Roche, and Bayer Schering; lecture fees from Novartis, Teva Pharmaceutical Ind. Ltd., Sanofi-Aventis, Merck, Biogen Dompè, Bayer Schering, and Serono Symposia International Foundation; and trial grant support from Novartis, Teva Pharmaceutical Ind. Ltd., Sanofi-Aventis, Receptos, Biogen Idec, Genentech-Roche, Merck, Biogen Dompè, and Bayer Schering. **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. **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. **PV** has received honoraria or consulting fees from Biogen, Sanofi-Genzyme, Bayer, Novartis, Merck KGaA, Celgene, Roche and Almirall; and research support from Biogen, Sanofi-Genzyme, Bayer, and Merck KGaA. **FD** is an employee of EMD Serono Research & Development Institute Inc., a business of Merck KGaA, Darmstadt, Germany. **BK** and **DJ** are employees of Merck KGaA, Darmstadt, Germany.

The CLARITY study: NCT00213135. The CLARITY Extension study: NCT00641537.

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