

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

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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

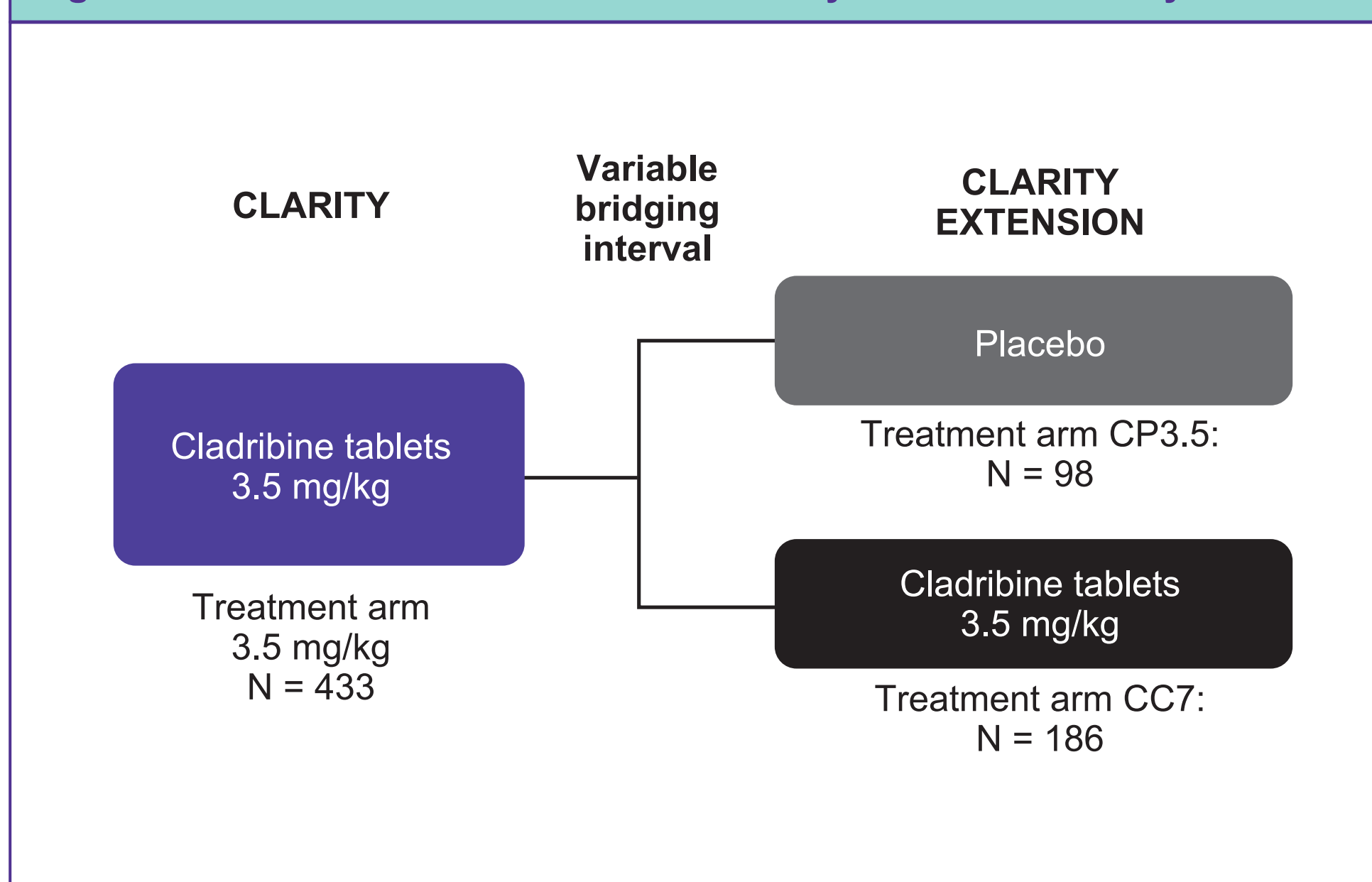
- To evaluate *post hoc*, long-term disease stability assessed by the EDSS score after treatment with CT3.5 in patients with RRMS enrolled in CLARITY and CLARITY Extension.

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.
 - CLARITY Extension was not a pre-planned 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

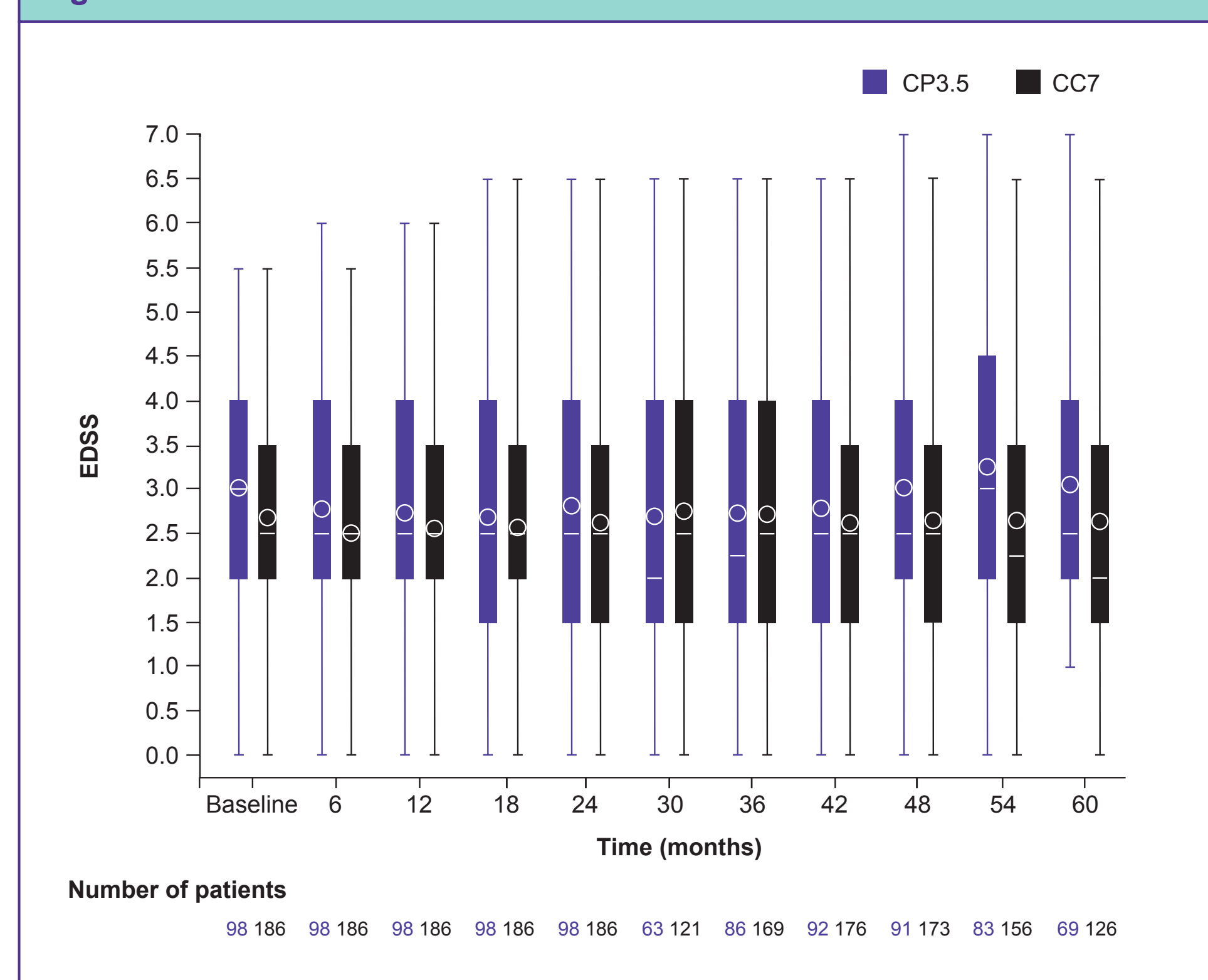
- This was a *post hoc* exploratory analysis of a subset of patients who completed 6 years of follow-up.
- EDSS score over time was descriptively analysed (median, 95% confidence interval [CI]) at 6-monthly intervals, overall and by bridging interval length (≤ 43 weeks versus > 43 weeks).
- Improvement, 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 a variable bridging interval of ≤ or > 43 weeks.

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

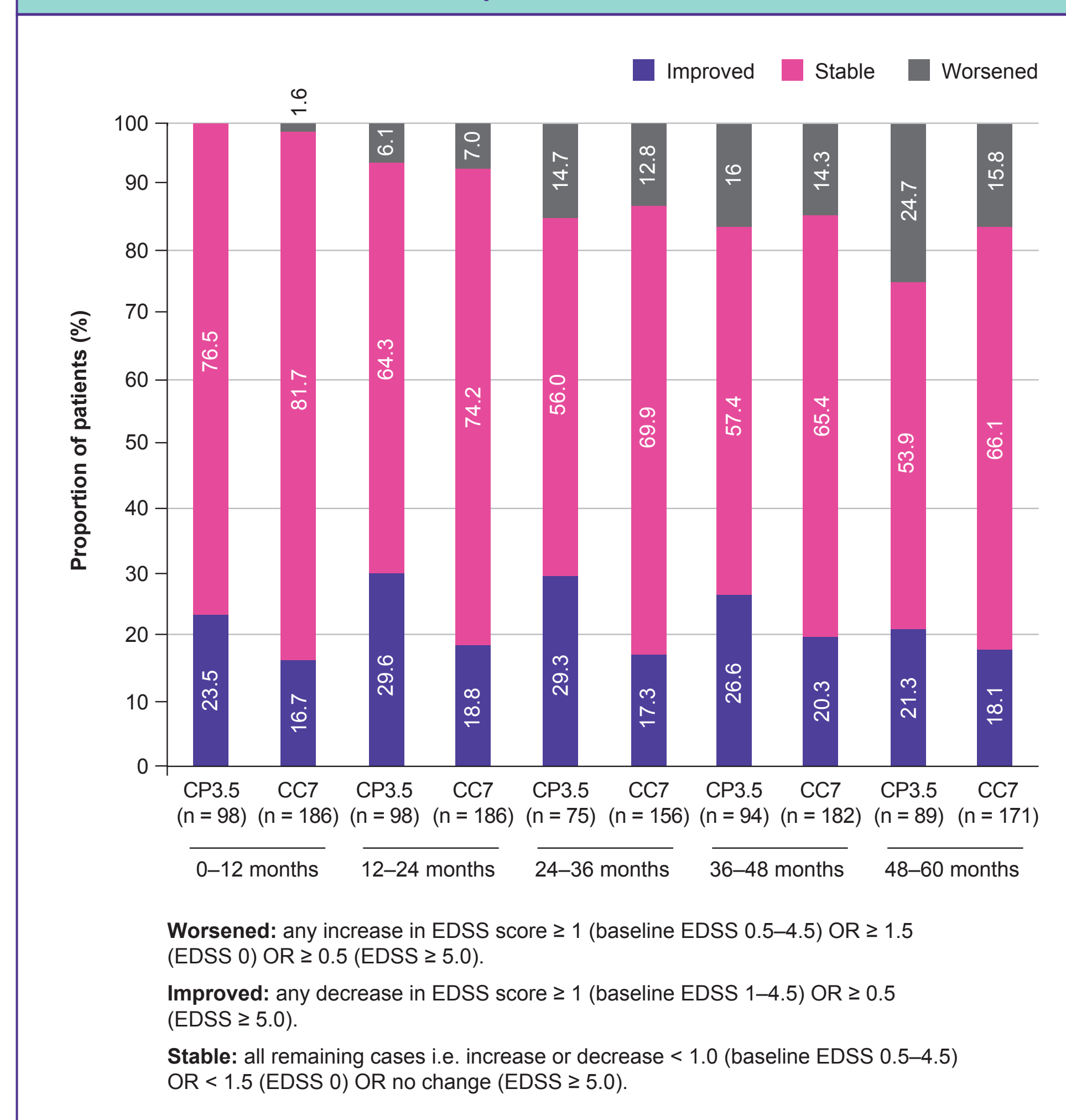


Line = Median. Circles = Mean. Box = Q1, Q3. Error bars reflect the minimum and maximum EDSS score. CP3.5, CT3.5 CLARITY, placebo Extension; CC7, CT3.5 CLARITY, CT3.5 CLARITY Extension; EDSS, Expanded Disability Status Scale.

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).

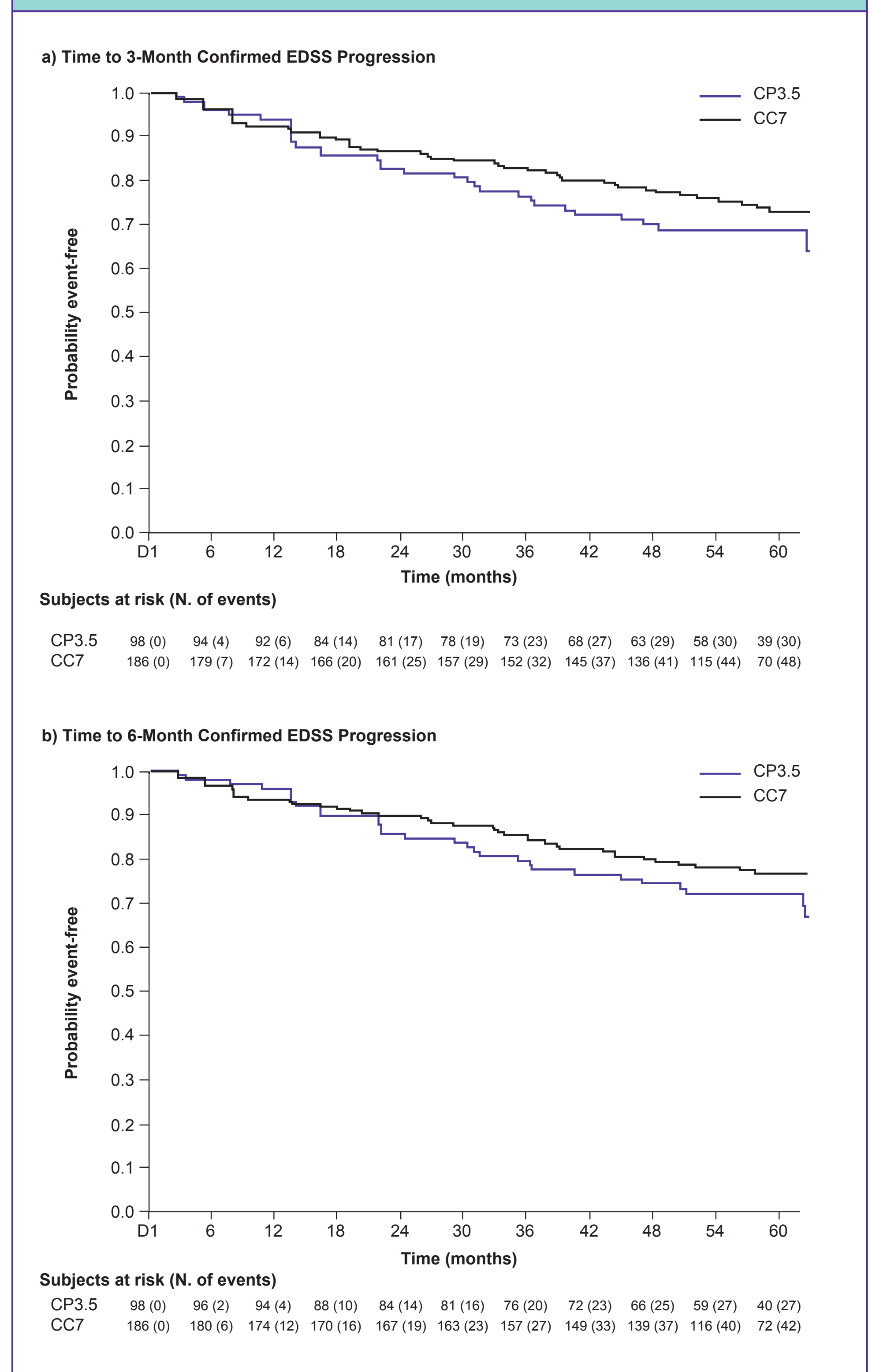
Stable: all remaining cases i.e. increase or decrease < 1.0 (baseline EDSS 0.5–4.5) OR < 1.5 (EDSS 0) OR no change (EDSS ≥ 5.0).

CP3.5, CT3.5 CLARITY, placebo Extension; CC7, CT3.5 CLARITY, CT3.5 CLARITY 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



CP3.5, CT3.5 CLARITY, placebo Extension; CC7, CT3.5 CLARITY, CT3.5 CLARITY 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

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

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DISCLOSURES

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