Poster No. 66

Durability of NEDA-3 Status in Patients with Relapsing Multiple Sclerosis Receiving Cladribine Tablets: CLARITY Extension

G. Giovannoni[1], B. Keller[2], E. Merino[2]

[1]Queen Mary University of London, Blizard Institute, Barts and The London School of Medicine and Dentistry, London, UK; [2]Merck KGaA, Darmstadt, Germany.

INTRODUCTION

- In the CLARITY study, Cladribine Tablets 10 mg (3.5 mg/kg cumulative dose over 2 years; referred to as Cladribine Tablets 3.5 mg/kg) showed strong efficacy vs. placebo over 2 years in patients with relapsing multiple sclerosis (RMS).[1]
- No Evidence of Disease Activity-3 (NEDA-3) status was achieved in significantly more patients receiving Cladribine Tablets 3.5 mg/kg in CLARITY (47%) than those receiving placebo (17%; $P < 0.0001$).[2]

OBJECTIVE

- This was a *post hoc* analysis to determine NEDA-3 status in patients who received Cladribine Tablets 3.5 mg/kg in CLARITY and who were then randomised in CLARITY Extension to either placebo (CP3.5 group) or Cladribine Tablets 3.5 mg/kg (CC7.0 group).

METHODS

- The study design for CLARITY and CLARITY Extension is shown in **Figure 1A**.
- Patients were retrospectively analysed for NEDA-3 status (defined as patients with no relapse, no 6-month Expanded Disability Status Scale [EDSS] progression and no T1 gadolinium-enhancing [Gd+] or active T2 lesions) in the first year of CLARITY Extension for the CP3.5 (n = 98) and CC7.0 groups (n = 186).
- Baseline demographics for the overall patient groups included in this analysis are shown in **Table 1**.

Table 1. Baseline Demographics and Disease Characteristics in CLARITY Extension for Patient Groups Included in the Analysis (ITT Population)

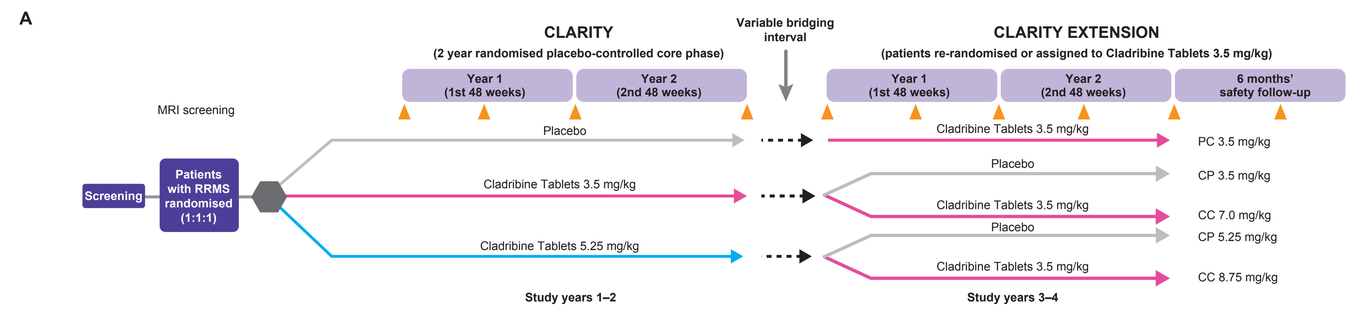
	CP 3.5 mg/kg (n = 98)	CC 7 mg/kg (n = 186)
Age, years	40.7 (10.7)	40.6 (10.5)
Female, n (%)	67 (68.4)	124 (66.7)
White, n (%)	96 (98.0)	181 (97.3)
Weight, kg	67.93 (14.89)	68.91 (14.09)
DMD use in 3 months prior to CLARITY Extension day 1, n (%)	0	0
Relapsed between CLARITY and Extension, n (%)	9 (9.2)	17 (9.1)
Disease duration[a], years	10.1 (6.7)	10.4 (7.1)
Median EDSS score (min; max)	2.5 (0.0; 6.5)	2.5 (0.0; 6.5)
Interval between studies[b], weeks	41.2 (26.1)	42.1 (25.4)
Median interval between studies (min, max), weeks	41.3 (0.1; 116.0)	41.4 (0.4; 115.3)

Data are mean (SD), unless otherwise stated. [a]Time from first attack to CLARITY Extension Study Day 1. [b]Duration of the gap between the last visit date in the CLARITY treatment period and the randomisation date in CLARITY Extension.

CC7.0, patients randomised to Cladribine Tablets 3.5 mg/kg in both CLARITY and CLARITY Extension; **CP3.5**, patients randomised to Cladribine Tablets 3.5 mg/kg in CLARITY and placebo in CLARITY Extension; **EDSS**, Expanded Disability Status Scale; **ITT**, intent-to-treat.

- Bridging interval between CLARITY and CLARITY Extension was used as a proxy for when patients completed the first year of CLARITY Extension. Patients were categorised in the Year 3–4 group if they had a bridging interval of ≤ 43 weeks or in the Year 4–5 group for patients with a bridging interval of > 43 weeks (**Figure 1B**).
- After patients with unknown outcome were excluded, confirmed NEDA-3 status in the first year of CLARITY Extension for the Year 3–4 and Year 4–5 groups was known for:
  - **Year 3–4:** CP3.5 group, n = 54; CC7.0 group, n = 98.
  - **Year 4–5:** CP3.5 group, n = 40; CC7.0 group, n = 77
- Differences in NEDA-3 in the CP3.5 and CC7.0 group were analysed by logistic regression with treatment and bridging interval duration (continuous variable) as fixed effects.
- All analyses were *post hoc* and exploratory.

Figure 1. (A) CLARITY/CLARITY Extension Study Design and (B) Designation of Patients into the Year 3–4 or Year 4–5 Groups



Cladribine tablets 3.5 mg/kg over 2 years is the only approved dose.

†Intent-to-treat population.

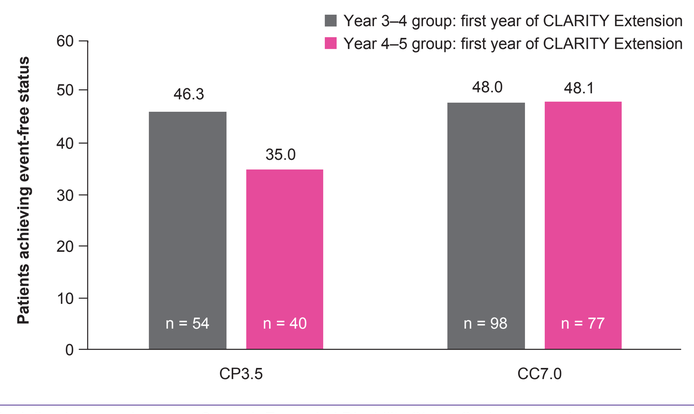
CC7.0, patients randomised to Cladribine Tablets 3.5 mg/kg in both CLARITY and CLARITY Extension; **CC8.75**, patients randomised to Cladribine Tablets 5.25 mg/kg in CLARITY and Cladribine Tablets 3.5 mg/kg in CLARITY Extension; **CP3.5**, patients randomised to Cladribine Tablets 3.5 mg/kg in CLARITY and placebo in CLARITY Extension; **CP5.25**, patients randomised to Cladribine Tablets 5.25 mg/kg in CLARITY and placebo in CLARITY Extension; **MRI**, magnetic resonance imaging; **PC3.5**, patients randomised to placebo in CLARITY and Cladribine Tablets 3.5 mg/kg in CLARITY Extension; **RRMS**, relapsing-remitting multiple sclerosis.

RESULTS

Proportion of patients achieving NEDA-3 status

- In the Year 3–4 group, annual NEDA-3 was achieved in 46% (25/54) of patients with known status in the CP3.5 group and 48% (47/98) in the CC7.0 group (**Figure 2**).
- For the Year 4–5 group, there was a numerical trend for a lower rate of annual NEDA-3 for patients in the CP3.5 group (35%; 14/40) than the CC7.0 group (48%; 37/77) (**Figure 2**).
- Adjusting for the length of the bridging interval, there was no significant difference between annual NEDA-3 in the CP3.5 (41.5%, 95% CI 32.4–60.0%) and CC7.0 (48.0%, 95% CI 40.2–64.4%) groups (odds ratio 1.3, 95% CI 0.8–2.2; $P = 0.31$).

Figure 2. NEDA-3 Status in the First Year of CLARITY Extension

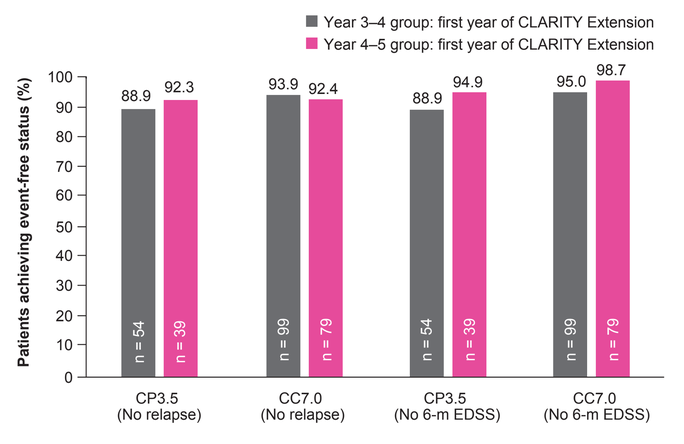


NEDA- defined as no relapse, no 6-month Expanded Disability Status Scale progression and no T1 gadolinium-enhancing or active T2 lesions.
Patients with unknown outcome excluded.
CC7.0, patients randomised to Cladribine Tablets 3.5 mg/kg in both CLARITY and CLARITY Extension; **CP3.5**, patients randomised to Cladribine Tablets 3.5 mg/kg in CLARITY and placebo in CLARITY Extension; **NEDA-3**, no evidence of diseases activity.

Proportion of patients achieving individual components of the NEDA-3 composite endpoint

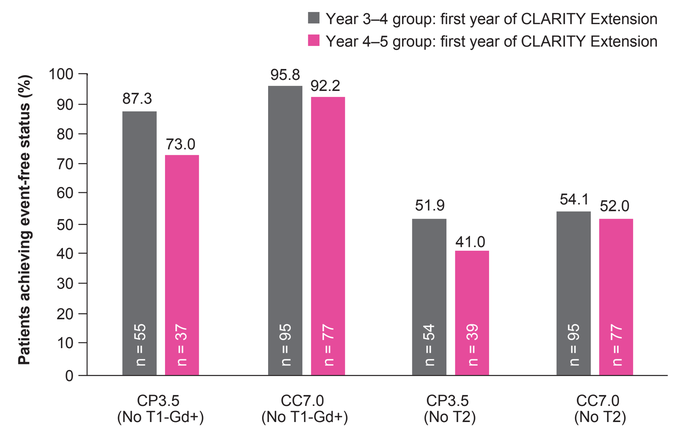
- As with NEDA-3 status, proportions of annual relapse-free, annual 6-month EDSS progression free (**Figure 3**) and freedom from T1 Gd+ and active T2 lesions (**Figure 4**) were largely similar, regardless of bridging interval duration.
  - The exception was the CP3.5 Year 4–5 group in which there were fewer patients free of T1 Gd+ and active T2 lesions compared to other groups (**Figure 4**).

Figure 3. Freedom From Relapse or 6-month EDSS Progression in the First Year of CLARITY Extension



Patients with unknown outcome excluded.
CC7.0, patients randomised to Cladribine Tablets 3.5 mg/kg in both CLARITY and CLARITY Extension; **CP3.5**, patients randomised to Cladribine Tablets 3.5 mg/kg in CLARITY and placebo in CLARITY Extension; **EDSS**, Expanded Disability Status Scale.

Figure 4. Freedom From T1 Gd+ or Active T2 Lesions in the First Year of CLARITY Extension



Patients with unknown outcome excluded.
CC7.0, patients randomised to Cladribine Tablets 3.5 mg/kg in both CLARITY and CLARITY Extension; **CP3.5**, patients randomised to Cladribine Tablets 3.5 mg/kg in CLARITY and placebo in CLARITY Extension; **Gd+**, Gadolinium-enhancing.

CONCLUSIONS

- **In this *post hoc* analysis, patients treated in CLARITY with Cladribine Tablets 3.5 mg/kg and with either placebo or Cladribine Tablets 3.5 mg/kg in CLARITY Extension experienced sustained benefits for NEDA-3, or its components.**
  - **NEDA-3 was lower in the CP3.5 Year 4–5 group than in the other groups, probably driven by lower rates of freedom from T1 Gd+ or T2 lesions.**
- **NEDA-3 outcomes, or its constituent elements, were not significantly different between patients in the Year 3–4 or Year 4–5 groups.**

REFERENCE

1. Giovannoni G, et al. *N Engl J Med.* 2010;362:416–426
2. Giovannoni G, et al. *Lancet Neurol.* 2011;10:329–37
3. Giovannoni G, et al. *Mult Scler.* 2017:1352458517727603. doi: 10.1177/1352458517727603

ACKNOWLEDGEMENTS

This study was sponsored by EMD Serono Inc, a business of Merck KGaA, Darmstadt, Germany (in the USA), and Merck Serono SA, Geneva, an affiliate of Merck KGaA Darmstadt, Germany (ROW). Medical writing assistance was provided by Ash Dunne of inScience Communications, Springer Healthcare, Chester, UK, and was funded by Merck KGaA, Darmstadt, Germany.

DISCLOSURES

GG has received speaker honoraria and consulting fees from Abbvie, Actelion, Almirall, Atara Bio, Bayer Schering Pharma, Biogen Idec, FivePrime, GlaxoSmithKline, GW Pharma, Merck, 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, Novartis, and Ironwood. **BK** and **EM** are employees of Merck KGaA, Darmstadt, Germany.

The CLARITY study: NCT00213135; The CLARITY Extension study: NCT00641537

Cladribine Tablets are approved by the European Commission for the treatment of adult patients with highly active relapsing multiple sclerosis (MS) as defined by clinical or imaging features.

GET POSTER PDF

Presented at the European Charcot Foundation (ECF) Congress 2018; 15 - 17 November 2018; Baveno, Italy.