Poster No. 38

An Exploratory Analysis of the Efficacy of Cladribine Tablets 3.5 mg/kg in Patients with Relapsing Multiple Sclerosis Stratified to Age Above and Below 45 years in the CLARITY Study

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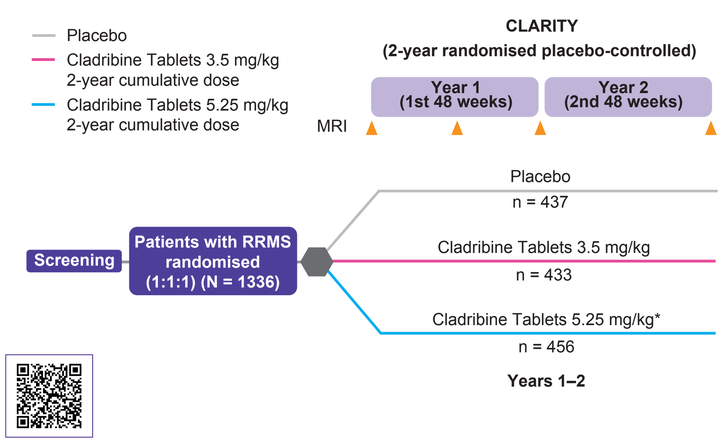
INTRODUCTION

- CLARITY, a large Phase III study (**Figure 1**) in patients with relapsing-remitting multiple sclerosis (RRMS), demonstrated that Cladribine Tablets 10 mg (3.5 mg/kg cumulative dose over 2 years; referred to as Cladribine Tablets 3.5 mg/kg), significantly reduced relapse rates, disability progression and outcomes assessed by magnetic resonance imaging (MRI) vs. placebo.[1]
- Compared to older age of onset, younger age of onset has been noted to predict greater future relapse and MRI activity in patients with MS.[2]
- Recent data have suggested a reduction in disease-modifying drug (DMD) efficacy in older patients.[3] If confirmed, this represents an important consideration for the management of older patients with MS.
- Therefore, it was deemed of interest to investigate the effect of age on the efficacy of Cladribine Tablets 3.5 mg/kg, using data from the CLARITY study.

Figure 1. CLARITY Study Design



*Cladribine Tablets 3.5 mg/kg over 2 years is the only approved dose.
MRI, magnetic resonance imaging; **RRMS**, relapsing-remitting multiple sclerosis.

OBJECTIVE

- The aim of this *post hoc* analysis was to evaluate the effect of Cladribine Tablets 3.5 mg/kg treatment in patients with RRMS > 45 or ≤ 45 years.

METHODS

- The CLARITY study enrolled patients aged 18–65 years with a definite diagnosis of RRMS:[1]
  - ≥ 1 relapse in the 12 months before study entry, but no relapses within the 28 days before entry
  - neurological lesions detectable by MRI consistent with MS
  - an Expanded Disability Status Scale (EDSS) score of 0–5.5.
- Patients were excluded from the study if two or more previous DMDs had failed or if they had received immunosuppressive therapy at any time before study entry or cytokine-based therapy, intravenous immune globulin therapy, or plasmapheresis within 3 months before study entry.
- In CLARITY, MRI scans were carried out at the pre-trial assessment and at Weeks 24, 48 and 96 (or early termination).
- A qualifying relapse was categorised by changes in Kurtzke Functional Systems Score and other specified clinical parameters.
  - Qualifying relapses were confirmed by an independent evaluating physician, blinded to study-group assignments.
- 'All' relapses included qualifying relapses and reported relapses that were not confirmed to meet the criteria for qualifying.
- The intention-to-treat population for the Cladribine Tablets 3.5 mg/kg and placebo treatment groups of CLARITY was stratified according to age: > 45 and ≤ 45 years.
- Efficacy analyses were conducted for endpoints of qualifying relapse, all relapses, mean and cumulative numbers of new T1 gadolinium-enhancing (Gd+), active T2 and combined unique (CU) lesions.
  - No evidence of disease activity (NEDA) was defined as qualifying relapse-free, 6-month confirmed EDSS progression-free, T1 Gd+ lesion-free, and active T2 lesion-free.
    - Patients who were missing data for one or more components of NEDA were reported as unknown.

RESULTS

Patients

- The aged-matched (> 45 or ≤ 45 years) patients in both the Cladribine Tablets 3.5 mg/kg or placebo treatment groups displayed similar baseline demographics and disease characteristics (**Table 1**).
- The overall analysis involved 870 patients randomised to placebo (n = 437) or Cladribine Tablets 3.5 mg/kg (n = 433):
  - A total of 221 patients were > 45 years (Cladribine Tablets 3.5 mg/kg; n = 103) and 649 were ≤ 45 years (Cladribine Tablets 3.5 mg/kg; n = 330).
  - There was a higher proportion of females in the older group (Cladribine Tablets 3.5 mg/kg; 77.7%) than in the younger group (Cladribine Tablets 3.5 mg/kg; 66.1%).
- A higher disease duration, higher baseline EDSS scores, and fewer patients with 3 or more relapses in the previous year were observed in the > 45 years subgroup.
- Patients aged ≤ 45 years experienced more relapses in the year prior to the study and had a higher number of T1 Gd+ lesions at baseline.

Table 1. Patient Demographics and Disease Characteristics by Treatment and Age Subgroups

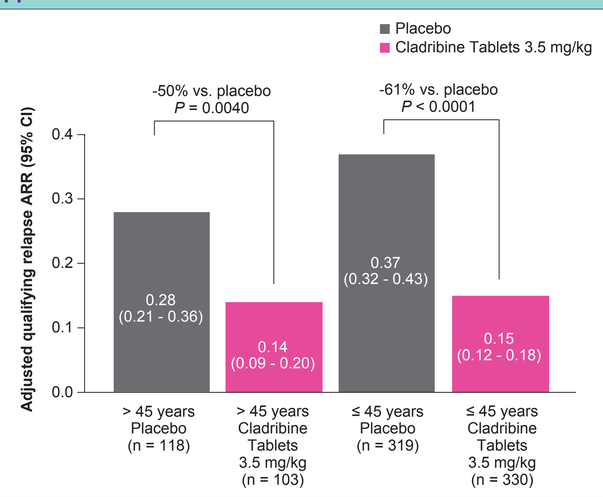
	Placebo		Cladribine Tablets 3.5 mg/kg	
	> 45 years n = 118	≤ 45 years n = 319	> 45 years n = 103	≤ 45 years n = 330
Age, years	51.1 (4.2)	34.1 (7.0)	51.7 (4.7)	33.7 (7.4)
Female, n (%)	90 (76.3)	198 (62.1)	80 (77.7)	218 (66.1)
Disease duration, years	8.02 (7.12)	4.14 (4.25)	7.43 (8.10)	3.82 (4.06)
Prior use of DMDs, n (%)	33 (28.0)	99 (31.0)	22 (21.4)	88 (26.7)
Relapses in prior 12 months, n (%)				
0	0	0	0	0
1	91 (77.1)	215 (67.4)	78 (75.7)	224 (67.9)
2	26 (22.0)	84 (26.3)	18 (17.5)	88 (26.7)
≥ 3	1 (0.8)	20 (6.3)	7 (6.8)	18 (5.5)
EDSS score	3.47 (1.22)	2.74 (1.29)	3.29 (1.24)	2.69 (1.22)
Number of T1 Gd+ lesions	0.3 (1.1)	1.0 (2.3)	0.3 (1.0)	1.2 (3.0)
Number of T2 lesions	23.3 (12.7)	28.8 (19.0)	24.5 (14.7)	25.6 (16.8)
T2 lesion volume	14.02 (12.51)	14.41 (13.37)	15.06 (17.58)	14.77 (15.89)

DMD, disease modifying drug; **EDSS**, Expanded Disability Status Scale; **Gd+**, gadolinium-enhancing; **SD**, standard deviation.
Data are presented as mean (SD) unless otherwise specified.

Relapses

- Comparison of the annualised relapse rate (ARR) for qualifying relapses at Week 96 showed that Cladribine Tablets 3.5 mg/kg was associated with a significant relative risk reduction vs. placebo in both age groups (**Figure 2**).
  - For patients aged > 45 years, qualifying ARR was 0.14 for Cladribine Tablets vs. 0.28 for placebo.
  - For patients aged ≤ 45 years, qualifying ARR was 0.15 for Cladribine Tablets vs. 0.37 for placebo.

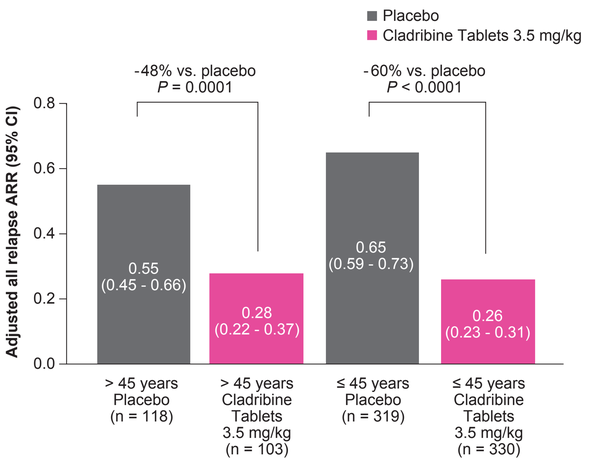
Figure 2. Estimated ARR for Qualifying Relapses in Patients Aged > 45 or ≤ 45 Years Treated with Cladribine Tablets 3.5 mg/kg or Placebo for 96 Weeks in CLARITY



Model adjusted for number of previous relapses and time on study.
ARR, annualised relapse rate; **CI**, confidence interval.

- The ARRs for all relapses (not confirmed as 'qualifying') were comparable to the qualifying ARRs for both age groups (**Figure 3**).
  - For patients aged > 45 years, all ARR was 0.28 for Cladribine Tablets vs. 0.55 for placebo.
  - For patients aged ≤ 45 years, all ARR was 0.26 for Cladribine Tablets vs. 0.65 for placebo.

Figure 3. Estimated ARR for All Relapses in Patients Aged > 45 or ≤ 45 Years Treated with Cladribine Tablets 3.5 mg/kg or Placebo for 96 Weeks in CLARITY



Model adjusted for number of previous relapses and time on study.
ARR, annualised relapse rate; **CI**, confidence interval.

- The treatment effect of Cladribine Tablets 3.5 mg/kg vs. placebo on qualifying and 'all' relapse rates was similar between age groups.

MRI Outcomes

- The mean number of new T1 Gd+ and cumulative new T1 Gd+ lesions at Week 96 was reduced with Cladribine Tablets 3.5 mg/kg compared to placebo in both age groups (**Table 2**).
- The mean number of active T2 lesions per patient per scan at Week 96 was significantly reduced with Cladribine Tablets 3.5 mg/kg vs. placebo in both age groups (**Table 2**):
  - Patients aged > 45 years: -0.167 (95% confidence interval [CI] -0.33, 0.00; $P < 0.0001$); patients aged ≤ 45 years: -0.667 (95% CI -0.67, -0.50; $P < 0.0001$).
- The mean number of CU lesions per patient per scan was also significantly reduced with Cladribine Tablets 3.5 mg/kg vs. placebo in both age groups (**Table 2**):
  - Patients > 45 years: -0.333 (95% CI -0.33, 0.00; $P < 0.0001$); patients ≤ 45 years: -0.667 (95% CI -1.00, -0.67; $P < 0.0001$).

Table 2. MRI Outcomes for CLARITY Patients Aged > 45 or ≤ 45 Years Treated with Cladribine Tablets 3.5 mg/kg or Placebo for 96 Weeks

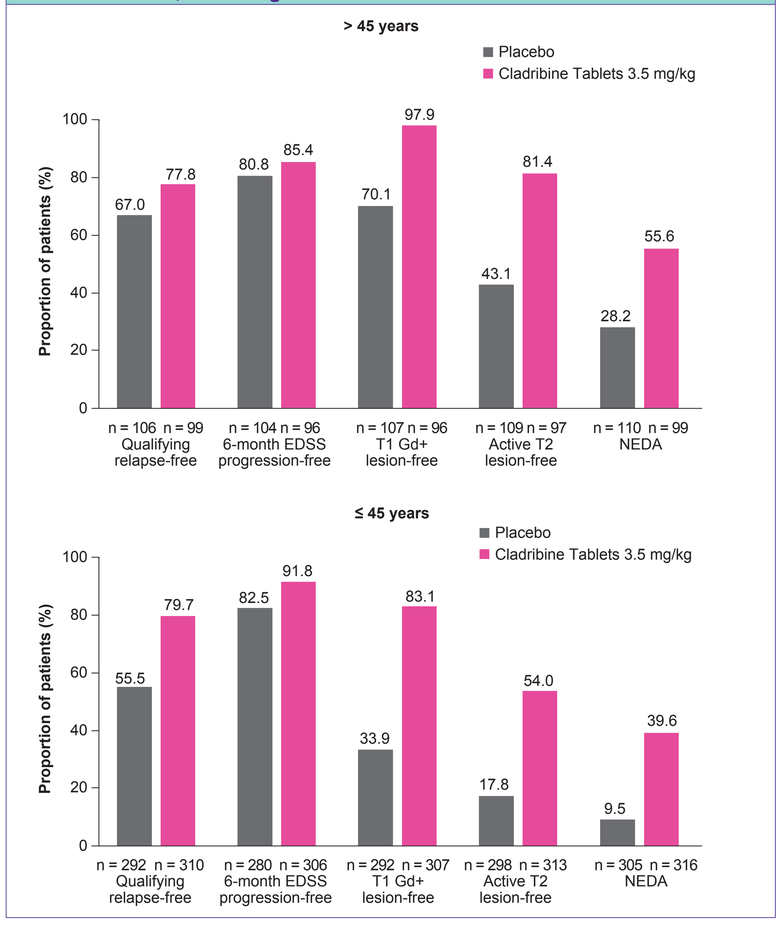
	Placebo		Cladribine Tablets 3.5 mg/kg	
	> 45 years n = 118	≤ 45 years n = 319	> 45 years n = 103	≤ 45 years n = 330
Number of new T1 Gd+ lesions/ patient/scan	0.41 (1.33)	1.02 (1.84)	0.01 (0.05)	0.12 (0.34)
Cumulative new T1 Gd+ lesions	1.17 (3.91)	2.70 (4.49)	0.02 (0.14)	0.33 (0.93)
Number of T2 lesions/ patient/scan	0.55 (0.79)	1.65 (2.14)	0.11 (0.26)	0.43 (0.73)
Number of CU lesions/ patient/scan	0.74 (1.51)	1.96 (2.59)	0.11 (0.26)	0.47 (0.78)

All data presented as mean (SD).
CU, combined unique; **Gd+**, gadolinium-enhancing; **MRI**, magnetic resonance imaging; **SD**, standard deviation.

NEDA

- For Cladribine Tablets 3.5 mg/kg, there were comparable increases in the proportions of patients fulfilling the individual components of NEDA in both age subgroups compared with placebo (**Figure 4**).
- In the > 45 and ≤ 45 years subgroups (among patients with known status), 55.6% and 39.6%, respectively, of patients treated with Cladribine Tablets 3.5 mg/kg achieved NEDA status compared with 28.2% and 9.5% respectively, of placebo recipients.
- The odds ratio for achieving NEDA were significantly more favourable for Cladribine Tablets vs. placebo in both age subgroups:
  - Patients aged > 45 years: 3.19 (95% CI 1.79, 5.66; $P < 0.0001$); patients aged ≤ 45 years: 6.23 (95% CI 3.99, 9.71; $P < 0.0001$).

Figure 4. Effects of Placebo and Cladribine Tablets 3.5 mg/kg on the Proportions of Patients Aged > 45 or ≤ 45 Years, who Fulfilled the Individual Components of NEDA at Week 96, Excluding Unknowns



EDSS, Expanded Disability Status Scale; **Gd+**, gadolinium-enhancing; **NEDA**, no evidence of disease activity.

CONCLUSIONS

- **Cladribine Tablets 3.5 mg/kg treatment was efficacious in patients regardless of age with respect to reduction of relapse frequency, number of MRI lesions and NEDA.**
  - **More patients were free from relapse and EDSS progression in the ≤ 45 years group than the > 45 years group.**
- **These data are consistent with previous analyses from CLARITY using a different age cut-off and with results from the overall study population.**

REFERENCES

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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, 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. **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. **SC** has received honoraria for lectures/ consultations from Merck, 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. **PS-S** has served on advisory boards for Biogen, Merck, Novartis, Teva, MedDay Pharmaceuticals, and GSK; on steering committees or independent data monitoring boards in trials sponsored by Merck, Teva, GSK, and Novartis; has received speaker honoraria from Biogen Idec, Merck, Teva, Sanofi-Aventis, Genzyme, and Novartis. His department has received research support from Biogen, Merck, Teva, Novartis, Roche, and Genzyme. **PV** has received honoraria or consulting fees from Biogen, Sanofi-Genzyme, Bayer, Novartis, Merck, Celgen, Roche and Almirall; and research support from Biogen, Sanofi-Genzyme, Bayer, and Merck. **BK** and **EVdC** are employees of Merck KGaA, Darmstadt, Germany.

The CLARITY study: NCT00213135

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.

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