Age-related efficacy of cladribine tablets in patients with relapsing-remitting MS in the CLARITY Extension study

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Abbreviations: ARR, annualized relapse rate; **CC**, cladribine-cladribine; **CI**, confidence interval; **CP**, cladribine-placebo; **EDA**, evidence of disease activity; **EDSS**, expanded disability status scale; **Gd+**, gadolinium-enhancing; **mo**, month; **MRI**, magnetic resonance imaging; **NEDA**, no evidence of disease activity; **RRMS**, relapsing-remitting multiple sclerosis; **SD**, standard deviation

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BACKGROUND INFORMATION

In the CLARITY study, treatment with cladribine tablets 10 mg (3.5 mg/kg cumulative dose over 2 years) demonstrated significant improvement over placebo on clinical and MRI efficacy outcomes in patients with RRMS[1]

In the CLARITY Extension study, treatment with an additional two years of either cladribine tablets 3.5 mg/kg or placebo following the initial two years of cladribine tablets 3.5 mg/kg in CLARITY produced similar durable clinical benefits[2]

In prior *post hoc* analyses of CLARITY, treatment with cladribine tablets 3.5 mg/kg for patients aged ≤40 or >40 years resulted in similar efficacy outcomes,[3,4] and analogous results were found in a separate analysis of patients aged ≤30 or >30 years at enrollment[5]

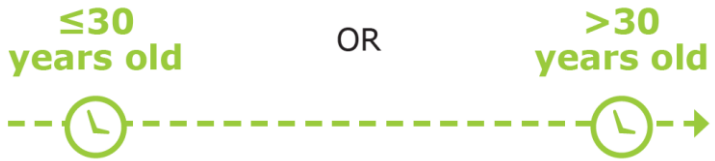
OBJECTIVE

This *post hoc* analysis examines the efficacy of

cladribine tablets 3.5 mg/kg

during **CLARITY Extension**

in patients who were



at **CLARITY** enrollment

Abbreviations: ARR, annualized relapse rate; **CC**, cladribine-cladribine; **CI**, confidence interval; **CP**, cladribine-placebo; **EDA**, evidence of disease activity; **EDSS**, expanded disability status scale; **Gd+**, gadolinium-enhancing; **mo**, month; **MRI**, magnetic resonance imaging; **NEDA**, no evidence of disease activity; **RRMS**, relapsing-remitting multiple sclerosis; **SD**, standard deviation

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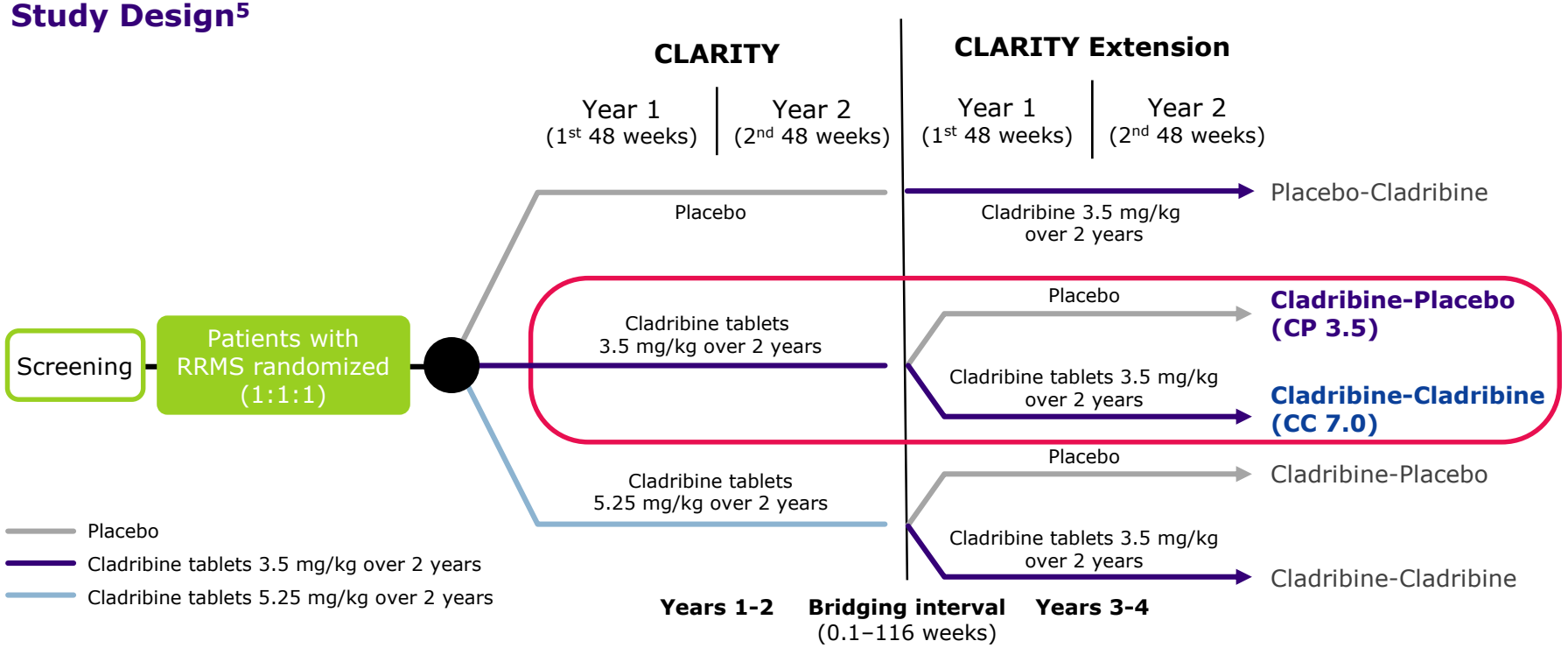
METHODS

Patients who completed CLARITY were eligible to participate in CLARITY Extension if they had normal lymphocyte counts and other hematological results within 28 days of the first dose[2]

Post-hoc analyses were performed at Year 2 of CLARITY Extension (**Week 96**) by age subgroup (**≤30** and **>30** years at CLARITY entry), a relatively young age cut-off

Study Design[5]



Endpoints

- Relapse
- 3- and 6-month confirmed EDSS progression
- MRI activity
- NEDA (no relapse, 3- or 6-month confirmed EDSS progression, or MRI activity)

Note: Cladribine tablets 10 mg (3.5 mg/kg cumulative dose over 2 years) is the only approved dose

Abbreviations: ARR, annualized relapse rate; **CC**, cladribine-cladribine; **CI**, confidence interval; **CP**, cladribine-placebo; **EDA**, evidence of disease activity; **EDSS**, expanded disability status scale; **Gd+**, gadolinium-enhancing; **mo**, month; **MRI**, magnetic resonance imaging; **NEDA**, no evidence of disease activity; **RRMS**, relapsing-remitting multiple sclerosis; **SD**, standard deviation

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RESULTS

The difference in the proportion of male patients between age cohorts (≤30 years vs. >30 years) was greater in the CP 3.5 subgroup (43.5% vs. 28.0%) compared to the CC 7.0 subgroup (38.8% vs. 31.4%)

Patient disposition

	CP 3.5		CC 7.0	
	≤30 years	>30 years	≤30 years	>30 years
Subjects who were randomized, n	23	75	49	137
Male	43.5%	28.0%	38.8%	31.4%
Mean age, years (SD)	26.1 (3.8)	45.2 (7.6)	27.3 (3.3)	45.4 (7.7)
Subjects who discontinued from study medication, n (%)	6 (26.1%)	6 (8.0%)	7 (14.3%)	35 (25.5%)
Weeks on study from date of randomization, mean (SD)	111.5 (45.8)	125.5 (24.6)	127.3 (31.4)	120.7 (29.6)

Abbreviations: ARR, annualized relapse rate; **CC**, cladribine-cladribine; **CI**, confidence interval; **CP**, cladribine-placebo; **EDA**, evidence of disease activity; **EDSS**, expanded disability status scale; **Gd+**, gadolinium-enhancing; **mo**, month; **MRI**, magnetic resonance imaging; **NEDA**, no evidence of disease activity; **RRMS**, relapsing-remitting multiple sclerosis; **SD**, standard deviation

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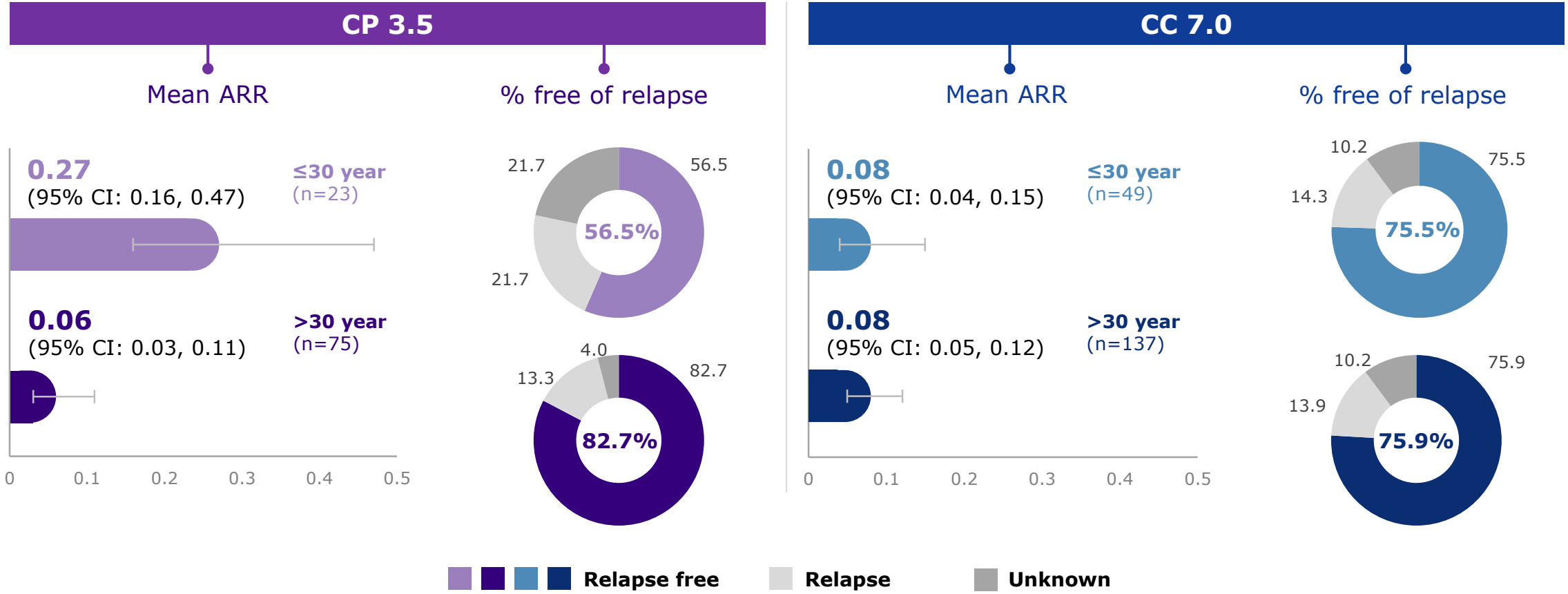
RESULTS

The ARR was greater in younger compared to older patients in the CP 3.5 subgroup, in line with the proportion of patients free of relapse. This difference was not seen in the CC 7.0 subgroup



Note: ARR estimated using a Poisson regression model of the relapse count as dependent variable with fixed effect for treatment group, region, and the log of time on study as offset variable. Dropouts were censored at the time of study discontinuation.

Abbreviations: ARR, annualized relapse rate; **CC**, cladribine-cladribine; **CI**, confidence interval; **CP**, cladribine-placebo; **EDA**, evidence of disease activity; **EDSS**, expanded disability status scale; **Gd+**, gadolinium-enhancing; **mo**, month; **MRI**, magnetic resonance imaging; **NEDA**, no evidence of disease activity; **RRMS**, relapsing-remitting multiple sclerosis; **SD**, standard deviation

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RESULTS

In the CP 3.5 subgroup, the mean cumulative number of T1 Gd+ and T2 lesions was greater in younger compared to older patients, in line with the proportion of patients free of T1 Gd+ and T2 lesions. This difference was not seen in the CC 7.0 subgroup

	CP 3.5		CC 7.0	
	≤30 years (n=23)	>30 years (n=75)	≤30 years (n=49)	>30 years (n=137)
Cumulative new T1 Gd+ lesions, adjusted mean (95% CI)	**0.54** (0.16, 1.79)	**0.27** (0.10. 0.73)	**0.02** (0.01, 0.08)	**0.02** (0.01, 0.06)
T1 Gd+ lesion free	**52.2%**	**73.3%**	**75.5%**	**83.9%**
T1 Gd+ lesion	26.1%	20.0%	10.2%	4.4%
T1 Gd+ lesion unknown	21.7%	6.7%	14.3%	11.7%
Cumulative active T2 lesions, adjusted mean (95% CI)	**2.95** (1.22, 7.10)	**1.40** (0.88, 2.22)	**1.36** (0.75, 2.45)	**1.12** (0.78, 1.61)
T2 lesion free	**21.7%**	**40.0%**	**38.8%**	**39.4%**
T2 lesion	60.9%	56.0%	51.0%	51.1%
T2 lesion unknown	17.4%	4.0%	10.2%	9.5%

Adjusted mean and associated 95% CI were estimated using a Negative Binomial regression model with fixed effect for treatment group, region and with the log of Number of Scan as the offset variable. Dropouts were censored at the time of study discontinuation.

Abbreviations: ARR, annualized relapse rate; **CC**, cladribine-cladribine; **CI**, confidence interval; **CP**, cladribine-placebo; **EDA**, evidence of disease activity; **EDSS**, expanded disability status scale; **Gd+**, gadolinium-enhancing; **mo**, month; **MRI**, magnetic resonance imaging; **NEDA**, no evidence of disease activity; **RRMS**, relapsing-remitting multiple sclerosis; **SD**, standard deviation

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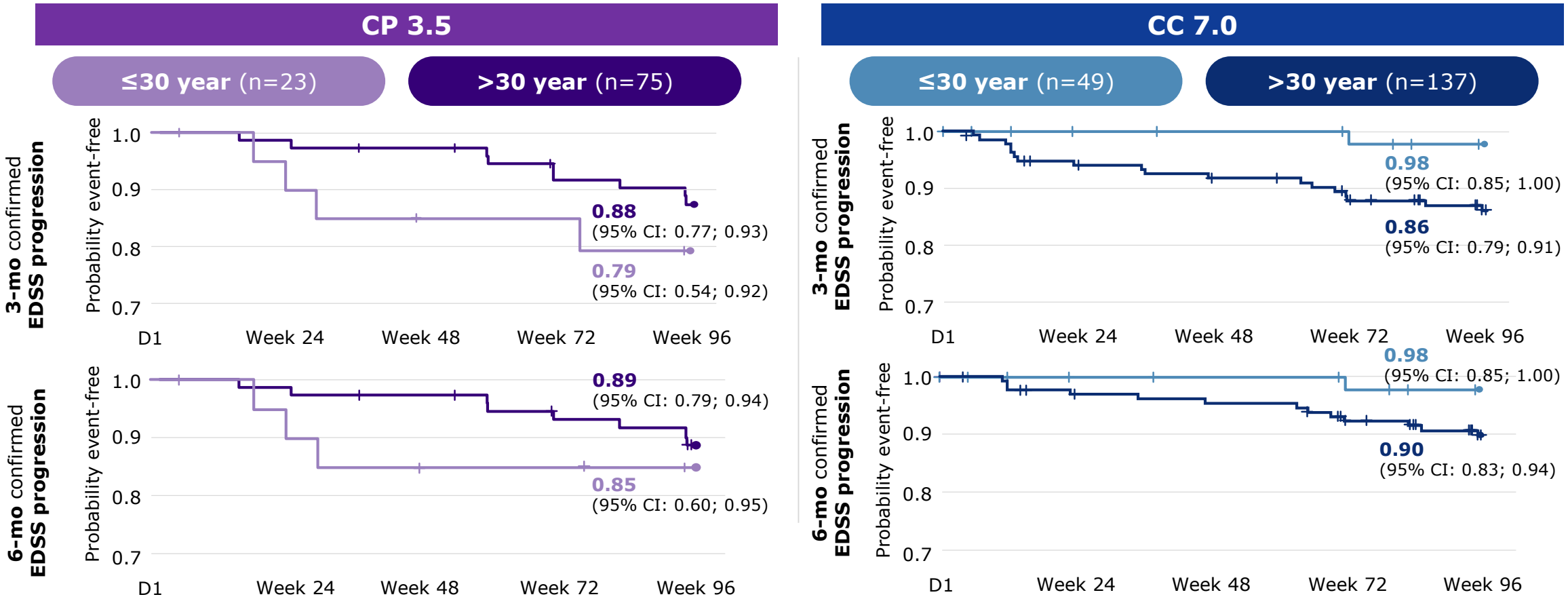
RESULTS

The probability of remaining free of 3- and 6-month confirmed EDSS progression at Week 96 was higher in older compared to younger patients in the CP 3.5 subgroup and in younger compared to older patients in the CC 7.0 subgroup



A 3- or 6-month confirmed increase in a subject's EDSS score occurs when a subject's EDSS score increases from baseline and the increase is sustained over consecutive visit(s) for a period equal to or greater than 3 or 6 months (i.e., 83 or 166 days).

Abbreviations: ARR, annualized relapse rate; **CC**, cladribine-cladribine; **CI**, confidence interval; **CP**, cladribine-placebo; **EDA**, evidence of disease activity; **EDSS**, expanded disability status scale; **Gd+**, gadolinium-enhancing; **mo**, month; **MRI**, magnetic resonance imaging; **NEDA**, no evidence of disease activity; **RRMS**, relapsing-remitting multiple sclerosis; **SD**, standard deviation

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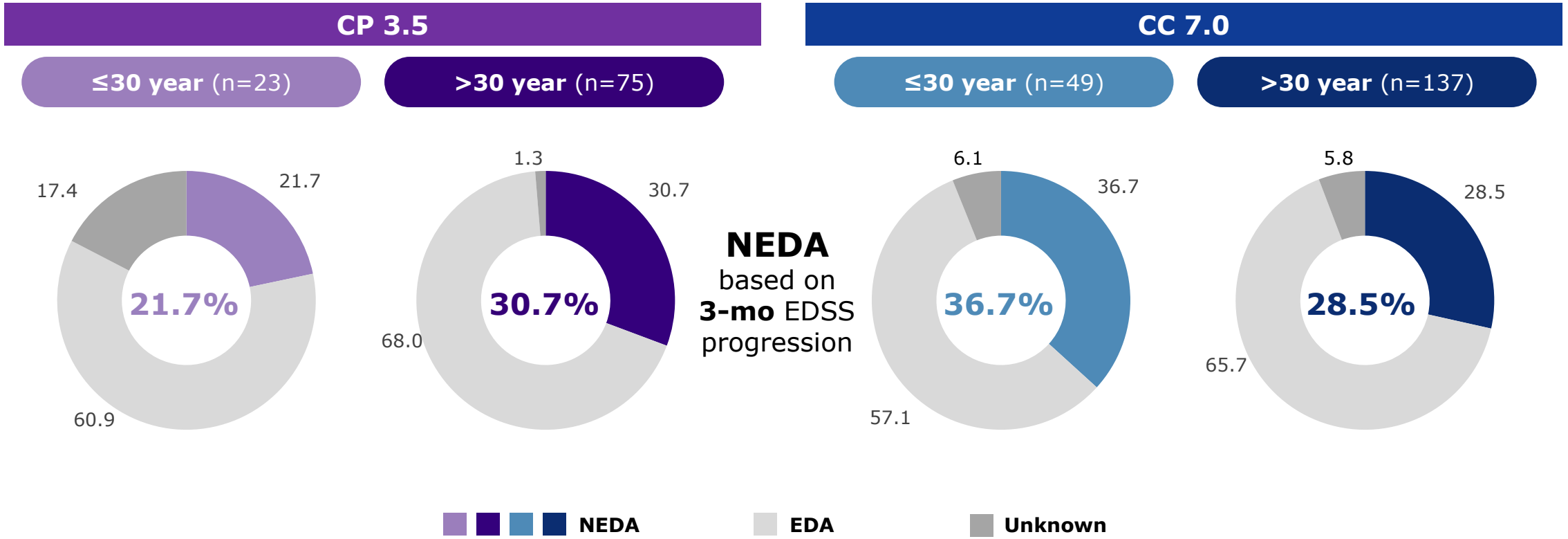
RESULTS

In the CP 3.5 subgroups, there was a higher proportion of patients with NEDA base on 3-month EDSS* in older compared to younger patients (driven by MRI). In the CC 7.0 subgroup, the proportions were higher in younger compared to older patients



NEDA: Patients with NEDA over 96 weeks for all 4 components: relapse, 3-month confirmed EDSS progression, new T1 Gd+ lesions, active T2 lesions; EDA: Patients with Disease Activity on ≥1 component are considered to have Evidence of Disease activity (EDA); Unknown: Patients with NEDA but missing ≥1 component. Dropouts were censored at the time of study discontinuation.
*NEDA results based on 6-mo EDSS progression were similar to those based on 3-mo EDSS progression.

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CONCLUSIONS

A substantial proportion of **younger** and **older** patients across cohorts achieved **NEDA** in **CLARITY Extension**

- As expected, younger patients showed higher disease activity.[6] The results suggest that they might benefit from therapy beyond 2 years (i.e. 4 years vs. 2 years)

STUDY LIMITATIONS

- Limitations, in particular within the CP 3.5 ≤30 years age cohort, include:
  - **Younger** patients with MS tend to experience increased rates of disease activity[6]
  - **Male** patients, who made up a larger proportion of the **≤30 year** group than the **>30 year** group in both **CP 3.5** (**43.5%** vs. **28.0%**) and **CC 7.0** (**38.8%** vs. **31.4%**), also tend to experience increased rates of disease activity[7]
  - **Subgroups** were **not balanced** in terms of **n**: CP 3.5 (≤30 year: n=23; >30 year: n=75) and CC 7.0 (≤30 year: n=49; >30 year: n=137). The observed differences may correspond to variability in line with the **small group sizes**
  - The proportion of patients for whom each endpoint was **unknown** was higher in the **CP 3.5 ≤30 years** age cohort compared with the other three age cohorts
- Overall, **CLARITY Extension** was not designed to compare treatment between **subgroups**
- Further, there was a **bridging interval** of variable duration (0.1–116 weeks) between **CLARITY** and **CLARITY Extension** during which data were not systemically captured

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