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Analysis of Lymphocyte Subsets in Younger and Older Patients with Multiple Sclerosis Treated with Cladribine Tablets

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SUMMARY



The objective of this *post hoc* analysis was to examine the effect of age at baseline on levels of lymphocyte subsets among patients with MS treated with cladribine tablets 3.5 mg/kg



Changes in levels of lymphocyte subsets (CD19+ B, CD4+ T and CD8+ T) over 96 weeks of treatment with placebo or cladribine tablets 3.5 mg/kg were examined by age at baseline



Pooled safety data of 1,564 patients from Phase 3 studies of cladribine tablets (CLARITY, CLARITY Extension and ORACLE-MS) were utilized for this analysis



By Week 96, cladribine tablets 3.5 mg/kg had similar effects on CD19+ B, CD4+ T and CD8+ T lymphocytes in younger and older patients with MS, with steady recovery following nadir

Abbreviations: CladT3.5, cladribine tablets 3.5 mg/kg, cumulative dose over 2 years; DMT, disease-modifying therapy; IQR, interquartile range; MS, multiple sclerosis; SD, standard deviation.

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DISCLOSURES & ACKNOWLEDGMENTS

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CL: employee of EMD Inc. Mississauga, ON, Canada, an affiliate of Merck KGaA, Darmstadt, Germany.

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Abbreviations: CladT3.5, cladribine tablets 3.5 mg/kg, cumulative dose over 2 years; **DMT**, disease-modifying therapy; **IQR**, interquartile range; **MS**, multiple sclerosis; **SD**, standard deviation.

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BACKGROUND INFORMATION

- Cladribine tablets 10 mg (3.5 mg/kg cumulative dose over 2 years) are approved in >80 countries for various indications related to relapsing forms of MS¹
- Cladribine tablets have been evaluated as part of an extensive clinical development program, including:
 - CLARITY and ORACLE-MS, which were 96-week, Phase 3, placebo-controlled studies of patients with relapsing-remitting MS and a first clinical demyelinating event, respectively^{2,3}
 - CLARITY Extension, which was a 120-week study that investigated long-term safety and efficacy of cladribine tablets 3.5 mg/kg versus placebo in eligible patients who completed CLARITY⁴
 - Only patients who received placebo in CLARITY and cladribine tablets 3.5 mg/kg in CLARITY Extension were included in this analysis
- Cladribine is a prodrug that preferentially reduces B and T lymphocyte levels^{1,5}
 - Consistent with its mechanism of action, lymphopenia (Grade ≥ 1) has been reported in ~90% of patients treated with cladribine tablets 3.5 mg/kg over 2 years¹
- As aging is associated with a decline in immune function,⁶ the effect of DMTs may vary in older versus younger patients with MS

Abbreviations: CladT3.5, cladribine tablets 3.5 mg/kg, cumulative dose over 2 years; **DMT**, disease-modifying therapy; **IQR**, interquartile range; **MS**, multiple sclerosis; **SD**, standard deviation.

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OBJECTIVE

To characterize the effect of age at baseline (≤ 50 years vs. > 50 years) on levels of lymphocyte subsets among patients treated with cladribine tablets 3.5 mg/kg



METHODS

- This was a *post hoc* analysis of the combined safety populations in the CLARITY, CLARITY Extension, and ORACLE-MS studies²⁻⁴
- A total of 1,564 patients were included in the analysis
 - **Age ≤ 50** : placebo: N=566; cladribine tablets 3.5 mg/kg: N=813
 - **Age > 50** : placebo: N=75; cladribine tablets 3.5 mg/kg: N=110
- Changes in levels of lymphocyte subsets (CD19+ B, CD4+ T and CD8+ T) over 96 weeks of treatment (Year 1: Weeks 0–48; Year 2: Weeks 48–96) with placebo or cladribine tablets 3.5 mg/kg were examined by age at baseline (≤ 50 years vs. > 50 years)
- All analyses were performed using SAS[®] software version 9.4 or higher

Abbreviations: CladT3.5, cladribine tablets 3.5 mg/kg, cumulative dose over 2 years; DMT, disease-modifying therapy; IQR, interquartile range; MS, multiple sclerosis; SD, standard deviation.

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RESULTS

- Baseline demographics and disease characteristics were generally well balanced between age groups in the cladribine studies
- Compared with the Age ≤50 group, the Age >50 group had*:
 - a higher proportion of women
 - longer disease duration
 - larger proportion of patients with one relapse at baseline

	Age ≤50 years		Age >50 years	
	Placebo (N=566)	CladT3.5 (N=813)	Placebo (N=75)	CladT3.5 (N=110)
Age, years, mean (SD)	34.9 (8.0)	34.7 (8.4)	54.3 (3.1)	54.6 (3.7)
Female, n (%)	367 (64.8)	531 (65.3)	57 (76.0)	81 (73.6)
Disease duration, years, median (range)	6.4 (0.4–31.3) ^a	6.6 (0.3–32.8) ^b	12.7 (0.5–39.5) ^c	11.4 (0.4–42.3) ^d
<3 years, n (%)	90 (24.5)	125 (21.5)	7 (10.3)	8 (7.8)
3–10 years, n (%)	172 (46.9)	291 (50.0)	22 (32.4)	34 (33.0)
>10 years, n (%)	105 (28.6)	166 (28.5)	39 (57.4)	61 (59.2)
Prior use of DMT				
No DMTs	450 (79.5)	650 (80.0)	60 (80.0)	89 (80.9)
1 DMT	91 (16.1)	128 (15.7)	11 (14.7)	16 (14.5)
≥2 DMTs	25 (4.4)	35 (4.3)	4 (5.3)	5 (4.5)
Number of relapses at baseline, n (%)				
0	201 (35.5)	382 (47.0)	7 (9.3)	37 (33.6)
1	254 (44.9)	305 (37.5)	52 (69.3)	58 (52.7)
≥2	111 (19.6)	126 (15.5)	16 (21.3)	15 (13.6)

^an=367; ^bn=582; ^cn=68; ^dn=103

*Statistical testing to examine differences in the two age groups was not conducted due to multiplicity and low sample size

Abbreviations: CladT3.5, cladribine tablets 3.5 mg/kg, cumulative dose over 2 years; **DMT**, disease-modifying therapy; **IQR**, interquartile range; **MS**, multiple sclerosis; **SD**, standard deviation.

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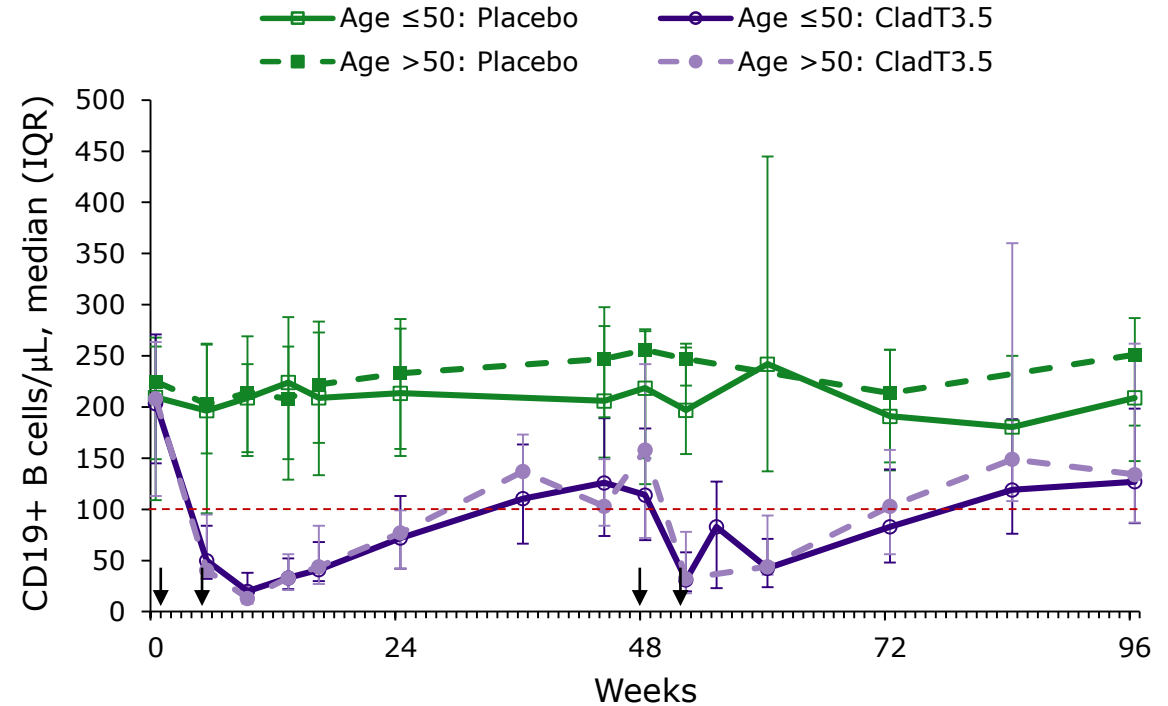


RESULTS

Cladribine tablets 3.5 mg/kg had a similar effect on CD19+ B lymphocytes among older and younger patients with MS

Following treatment with cladribine tablets 3.5 mg/kg:

- **Year 1 nadir occurred at Week 9** in both age groups
 - Median (IQR) for:
 - Age ≤50: 20 (10, 38) cells/μL
 - Age >50: 13 (8, 24) cells/μL
 - Levels recovered to normal range by Week 48
- **Year 2 nadir occurred at Week 52** in both age groups
 - Median (IQR) for:
 - Age ≤50: 31 (20, 58) cells/μL
 - Age >50: 33 (18, 78) cells/μL
 - Levels recovered to normal range by Week 96



Reference line (red) represents 100 cells/μL. Treatment weeks are indicated by arrows. Only visits with a sample size ≥10 are shown (No data plotted for Age ≤50: Placebo [Weeks 36 and 55]; Age >50: Placebo [Weeks 36, 55, 60 and 84]; Age >50: CladT3.5 [Week 55]).

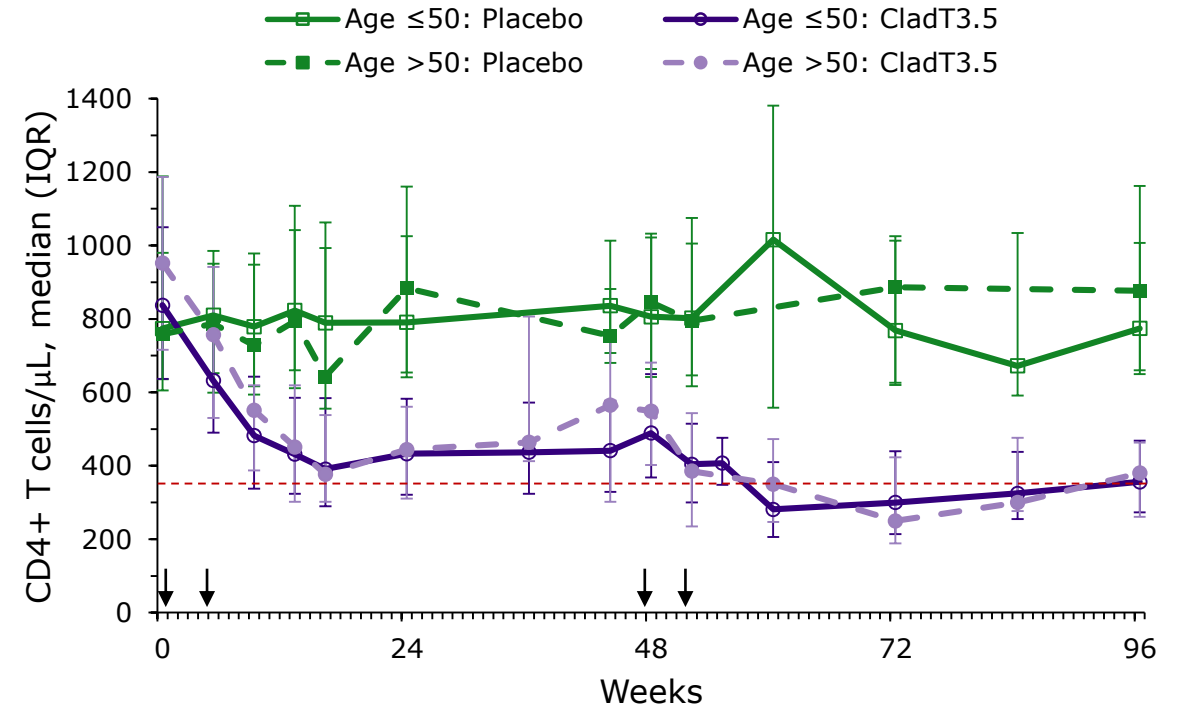


RESULTS

Cladribine tablets 3.5 mg/kg had a similar effect on CD4+ T lymphocytes among older and younger patients with MS

Following treatment with cladribine tablets 3.5 mg/kg:

- **Year 1 nadir occurred at Week 16** in both age groups
 - Median (IQR) for:
 - Age ≤50: 391 (290, 584) cells/μL
 - Age >50: 377 (302, 538) cells/μL
 - Levels remained in normal range through Week 48
- **In Year 2, nadir was below normal range** in both age groups.
 - Median (IQR) for:
 - Age ≤50: 281 (206, 410) cells/μL at Week 60
 - Age >50: 250 (189, 423) cells/μL at Week 72
 - Levels recovered to normal range by Week 96



Reference line (red) represents 350 cells/μL. Treatment weeks are indicated by arrows. Only visits with a sample size ≥10 are shown (No data plotted for Age ≤50: Placebo [Weeks 36 and 55]; Age >50: Placebo [Weeks 36, 55, 60 and 84]; Age >50: CladT3.5 [Week 55]).

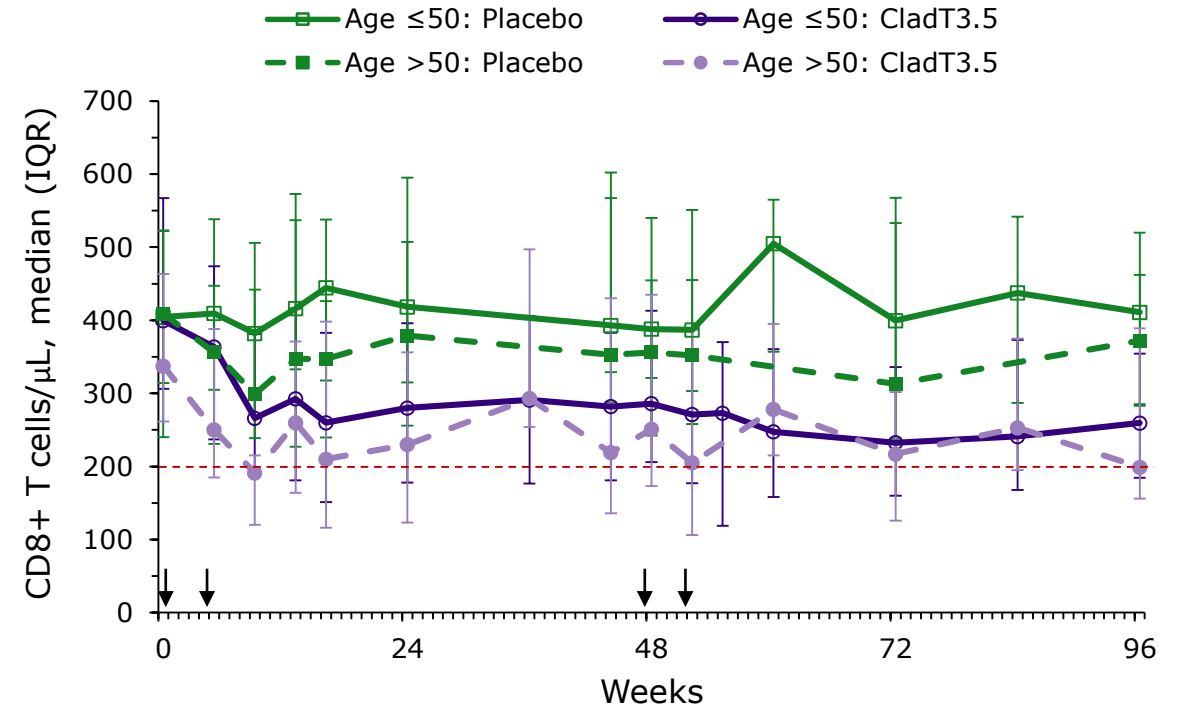


RESULTS

Cladribine tablets 3.5 mg/kg had a similar effect on CD8+ T lymphocytes among older and younger patients with MS

Following treatment with cladribine tablets 3.5 mg/kg:

- **Year 1 nadir occurred at Week 16 and Week 9 in the Age ≤50 and Age >50 groups, respectively**
 - Median (IQR) for:
 - Age ≤50: 260 (151, 383) cells/μL at Week 16 and remained in the normal range
 - Age >50: 191 (120, 215) cells/μL at Week 9, but recovered to normal range
- **Year 2 nadir occurred at Week 72 and Week 96 in the Age ≤50 and Age >50 groups, respectively**
 - Median (IQR) for:
 - Age ≤50: 233 (160, 336) cells/μL at Week 72 and remained in the normal range
 - Age >50: 199 (156, 389) cells/μL at Week 96, and remained in the normal range



Reference line (red) represents 200 cells/μL. Treatment weeks are indicated by arrows. Only visits with a sample size ≥10 are shown (No data plotted for Age ≤50: Placebo [Weeks 36 and 55]; Age >50: Placebo [Weeks 36, 55, 60 and 84]; Age >50: CladT3.5 [Week 55]).

Abbreviations: CladT3.5, cladribine tablets 3.5 mg/kg, cumulative dose over 2 years; DMT, disease-modifying therapy; IQR, interquartile range; MS, multiple sclerosis; SD, standard deviation.

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CONCLUSIONS

- **This *post hoc* analysis examined the impact of cladribine tablets 3.5 mg/kg on levels of lymphocyte subsets in older versus younger patients with MS**
- **Pooled safety data for this analysis consists of 1,564 patients from Phase 3 studies of cladribine tablets (CLARITY, CLARITY Extension and ORACLE-MS)**
- **Over 96 weeks of treatment, cladribine tablets 3.5 mg/kg had similar effects on CD19+ B, CD4+ T and CD8+ T lymphocyte subsets in older and younger patients with MS**
- **These results should be interpreted with caution due to differences in sample sizes between the two age groups**

Abbreviations: CladT3.5, cladribine tablets 3.5 mg/kg, cumulative dose over 2 years; DMT, disease-modifying therapy; IQR, interquartile range; MS, multiple sclerosis; SD, standard deviation.

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LAY SUMMARY

A lay summary for this poster is available.

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