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An Analysis of the Relationship Between Cladribine Dose and Risk of Malignancies in Patients with Multiple Sclerosis

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CONCLUSIONS

- Overall, there was no clear evidence of a dose effect of cladribine on malignancy risk in patients with multiple sclerosis based on >9500 patient years of cladribine exposure
  - Patients in the cladribine tablets >8.75 mg/kg group had a lower malignancy incidence than those in the >0–3.5 mg/kg group
- There was no strong evidence for an increase in risk of malignancy for patients receiving cladribine tablets 3.5 mg/kg versus placebo in the Monotherapy Oral cohort

INTRODUCTION

- Malignancy risk in patients with MS treated with cladribine tablets 10 mg (3.5 mg/kg cumulative dose over 2 years; referred to as cladribine tablets 3.5 mg/kg) was previously characterized in a Monotherapy Oral cohort including cumulative data up to February 2015[1]
- In clinical studies, an imbalance in the number of malignancies with cladribine tablets 3.5 mg/kg versus placebo was observed[1]

OBJECTIVES

- To provide a more detailed assessment of malignancy using safety data integrated from clinical trials and a safety follow-up registry (up to May 2017)
- To further characterize any potential malignancy risk with cladribine in patients with MS and investigate whether there is a dose-dependent risk

METHODS

- Integrated safety cohorts were as follows:
  - Monotherapy Oral: patients with MS receiving cladribine tablets at any dose as a monotherapy
  - All Exposed: patients with MS receiving any formulation or dose of cladribine to provide a larger cohort to identify rare events such as malignancies
- To compare malignancy risk between treatment with cladribine tablets and placebo, incidence risk difference and incidence risk ratios were calculated

RESULTS

Baseline Characteristics

- The Monotherapy Oral cohort included patients receiving placebo (N=641), cladribine tablets 3.5 mg/kg (N=923) and cladribine tablets 5.25 mg/kg (N=632)
- Patient characteristics were balanced between groups (**Table 1**)

RESULTS (cont.)

Table 1. Characteristics of Patients Included in the Monotherapy Oral Cohort

Patient characteristic	Placebo (N=641)	Cladribine tablets 3.5 mg/kg (N=923)	Cladribine tablets 5.25 mg/kg (N=632)
Patient-years*	2275	3754	2610
Time on study, weeks*; mean (SD)	185.21 (122.33)	212.22 (119.98)	215.51 (129.66)
Time on study, ≥96 weeks (~2 years), n (%)	493 (76.9)	784 (84.9)	514 (81.3)
Time on study, ≥192 weeks (~4 years), n (%)	204 (31.8)	430 (46.6)	278 (44.0)
Time on study, ≥432 weeks (~9 years), n (%)	18 (2.8)	23 (2.5)	26 (4.1)
Age, years†; mean (SD) Median Min; max	37.15 (9.83) 36.53 18.1; 64.2	37.84 (10.48) 37.62 18.2; 66.1	37.59 (10.02) 37.71 18.3; 66.0
Age ≤40 years, n (%)	396 (61.8)	540 (58.5)	365 (57.8)
Age >40 years, n (%)	245 (38.2)	383 (41.5)	267 (42.2)
Female, n (%)	424 (66.1)	612 (66.3)	422 (66.8)
Prior treatment with DMD, n (%)	131 (20.4)	184 (19.9)	130 (20.6)

*Cumulative to May 2017; †As reported at first dosing date.

Supplementary Appendix 1: Characteristics of Patients Included in the All Exposed Cohort

Malignancy by Treatment Group in the Monotherapy Oral Cohort

- A total of 10 malignancies were reported in patients treated with cladribine tablets 3.5 mg/kg, 6 in patients treated with cladribine tablets 5.25 mg/kg, and 3 in patients treated with placebo (**Table 2**)
  - The majority (8/10) of the malignancy events in the cladribine tablets 3.5 mg/kg group occurred within the first 4 years after cladribine exposure
- The confidence intervals for the risk differences included 0, and the confidence intervals for the risk ratios included 1.

Table 2. Incidence Rates, Risk Difference and Risk Ratio for Malignancies in Patients Treated with Cladribine Tablets or Placebo in the Monotherapy Oral Cohort

Patient characteristic	Placebo (N=641)	Cladribine tablets 3.5 mg/kg (N=923)	Cladribine tablets 5.25 mg/kg (N=632)
Patients with events/PY at risk	3 / 2271	10 / 3735	6 / 2588
Incidence per 100 PY (95% CI)	0.13 (0.04–0.41)	0.27 (0.14–0.50)	0.23 (0.10–0.52)
Risk difference per 100 PY versus placebo (95% CI)	–	0.14 (-0.14–0.38)	0.10 (-0.18–0.39)
Risk ratio versus placebo (95% CI)	–	2.03 (0.56–7.36)	1.76 (0.44–7.02)

RESULTS (cont.)

Supplementary Appendix 2: Schematic Diagram of the Patient Year Follow-up in Cladribine Tablets Clinical Trials

- Subgroups of patients randomized to cladribine tablets 3.5 mg/kg or 5.25 mg/kg in CLARITY or ORACLE MS, followed by additional treatment with cladribine tablets 3.5 mg/kg in CLARITY Extension or ORACLE MS (N=195 for each treatment group) were also investigated (**Table 3**)

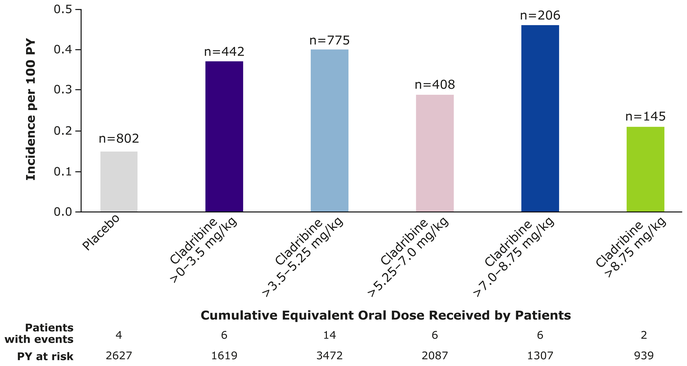
Table 3. Incidence Rates, Risk Difference and Risk Ratio for Malignancies in Patients Re-Treated with Cladribine Tablets in the Monotherapy Oral Cohort

	Entire follow-up period		Period following initiation of treatment in Year 3	
	Cladribine tablets 7.0 mg/kg (N=195)	Cladribine tablets 8.75 mg/kg (N=195)	Cladribine tablets 7.0 mg/kg (N=195)	Cladribine tablets 8.75 mg/kg (N=195)
Patients with events/PY at risk	7 / 1284	4 / 1276	7 / 773	4 / 774
Incidence per 100 PY (95% CI)	0.55 (0.26–1.14)	0.31 (0.12–0.84)	0.91 (0.43–1.90)	0.52 (0.19–1.38)
Risk difference per 100 PY versus placebo (95% CI)	0.41 (0.05–1.00)	0.18 (-0.13–0.68)	0.77 (0.26–1.73)	0.38 (-0.0053 –1.20)
Risk ratio versus placebo (95% CI)	4.13 (1.07–15.96)	2.37 (0.53–10.60)	6.85 (1.77–26.50)	3.91 (0.88–17.48)

Malignancy Stratified by Cladribine Dose in the All Exposed Cohort

- To further investigate any possible association between malignancies and exposure to cladribine, the occurrence of malignancies stratified by cumulative dose was assessed in a larger patient population: the All Exposed cohort
- Patients in the All Exposed cohort were exposed to cladribine (all doses and formulations, N=1976) or placebo (N=802)
- There was no evidence for an increase in malignancies with increasing cladribine exposure (**Figure 1**)

Figure 1. Dose Stratification of Incidence Rates for Malignancies in Patients Treated with Cladribine or Placebo in the All Exposed Cohort



	Placebo	>0–3.5 mg/kg	>3.5–5.25 mg/kg	>5.25–7.0 mg/kg	>7.0–8.75 mg/kg	>8.75 mg/kg
Patients with events	4	6	14	6	6	2
PY at risk	2627	1619	3472	2087	1307	939

Types of Malignancies Reported in the All Exposed Cohort

- The types of malignancies observed in the All Exposed cohort were investigated to identify whether there appeared to be any pattern related to cladribine
- The types of malignancies observed in the clinical program were typical of those observed in the general population
  - There was no clustering of malignancies and no increase in virally-induced malignancies, hematological malignancies, or non-melanoma skin cancers observed in the program

Abbreviations: CI, confidence interval; **DMD,** disease-modifying drug; **MS,** multiple sclerosis; **PY,** patient year; **SD,** standard deviation

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The CLARITY study: NCT00213135. The CLARITY Extension study: NCT00641537. The ORACLE-MS study: NCT00725985. The ONWARD study: NCT00436826. The PREMIERE registry: NCT01013350.

Reference: 1. Cook S, et al. *Mult. Scler. Relat. Disord.* 2019;29:157-167.

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