An Analysis of Malignancy Risk in the Clinical Development Programme of Cladribine Tablets in Patients With Relapsing Multiple Sclerosis

A. Galazka[1], A. Nolting[2], S. Cook[3], T. Leist[4], G. Comi[5], X. Montalban[6,8], C. Hicking[2], F. Dangond[7]

[1]Merck, Aubonne, Switzerland, a division of Merck KGaA, Darmstadt, Germany; [2]Merck KGaA, Darmstadt, Germany; [3]Rutgers, The State University of New Jersey, New Jersey Medical School, Newark, NJ, USA; [4]Division of Clinical Neuroimmunology, Thomas Jefferson University, Jefferson Medical College, PA, USA; [5]Department of Neurology and Institute of Experimental Neurology, Università Vita-Salute San Raffaele, Ospedale San Raffaele, Milan, Italy; [6]Department of Neurology-Neuroimmunology, Multiple Sclerosis Centre of Catalonia (Cemcat), Vall d'Hebron University Hospital, Vall d'Hebron, Barcelona, Spain; [7]EMD Serono, Inc., Billerica, MA, USA; [8]Division of Neurology, St. Michael's Hospital, University of Toronto, Toronto, ON, Canada

INTRODUCTION

- In patients with relapsing multiple sclerosis (RMS), treatment with two short annual courses of cladribine tablets (CT) 3.5 mg/kg cumulative dose produced significant improvements in clinical and neurological measures of disease activity.[1]
- Malignancy is an adverse event (AE) of special interest for immunosuppressive therapies. Although the lymphocyte reductions seen after each short annual treatment with cladribine tablets 3.5 mg/kg are transient (despite sustained clinical efficacy benefits),[2] it is of interest to assess the effects of treatment on safety.
- In CLARITY, there was a numerically higher incidence of malignancies in the CT group compared with the placebo group. However an independent review showed a similar rate of malignancy with cladribine tablets as with other disease modifying drugs (DMDs) in RMS clinical trials.[3]
- An integrated analysis based on the entirety of the clinical experience with oral cladribine in RMS (up to 8 years of follow up) can provide further insights into malignancy risk.

OBJECTIVES

- To assess malignancy risk with cladribine tablets 3.5 mg/kg and placebo in data from 3 Phase III trials and the PREMIERE registry, and to compare the incidence rate with a global malignancy database.

METHODS

- Safety data relating to treatment with cladribine tablets 3.5 mg/kg as oral monotherapy were taken from 3 Phase III studies that involved treatment with cladribine tablets 3.5 mg/kg and a prospective safety registry (**Table 1**).
- Malignancy case reports were taken from a monotherapy oral (MO) cohort which was analyzed using all malignancy events in 4 studies that involved treatment with cladribine tablets 3.5 mg/kg (**Table 1**).

Table 1. Summary of Clinical Studies in which Patients were Treated with Cladribine Tablets 3.5 mg/kg or Placebo in the Monotherapy Oral Cohort

Study	Design	Number*
CLARITY	Randomized, double blind	1326
CLARITY Extension	Re-randomized, double blind	806
ORACLE-MS	Randomized, double blind	617
PREMIERE	Prospective observational long-term safety registry	1133

* Number of patients randomized to double-blind treatment or enrolled into study.

- For this analysis of malignancies, data from the integrated clinical database (cut-off date 20 February 2015) and the Global Drug Safety database were used (cut-off date 05 November 2015).
- All cases with a reported preferred term within the Standardized Medical Dictionary for Regulatory Activities (MedDRA) Query "Malignant or Unspecified Tumors" (MedDRA version 17.1).
- All cases were adjudicated by an independent tumor review board on a case-by-case basis in a blinded fashion.
- Analysis of malignancy used a conservative approach:
  - Data from patients initially treated with cladribine and subsequently with placebo were analysed from the time of entry into the program as part of the cladribine group and never as part of the placebo group.

RESULTS

Patients

- The MO cohort included 923 patients (**Table 2**) who had been randomized to treatment with cladribine tablets 3.5 mg/kg (3433 patient years of exposure) and 641 patients treated with placebo (2026 patient years of exposure).

Table 2. Demographics of Patients Included in the Monotherapy Oral Cohort

	Placebo (n = 641)	Cladribine tablets 3.5 mg/kg (n = 923)
Patient years	2026	3433
Time on study in weeks, mean (SD)	164.92 (105.97)	194.05 (110.50)
Patients with time on study cumulative interval of at least 2 years, n (%)	486 (75.8)	772 (83.6)
Patients with time on study cumulative interval of at least 4 years, n (%)	181 (28.2)	395 (42.8)
Age (years), Mean (SD) Median Min; Max	36.6 (9.8) 36.0 18; 64	36.5 (10.3) 36.0 18; 65
Age ≤ 40 years, n (%)	415 (64.7)	592 (64.1)
Female, n (%)	424 (66.1)	612 (66.3)
Prior treatment with DMD, n (%)	131 (20.4)	184 (19.9)
Disease duration in years, mean (SD)	8.91 (7.39)	7.90 (6.91)

DMD, Disease Modifying Drug; **SD**, Standard Deviation.

Malignancy Rate Comparisons

- A total of 13 events were reported, 10 in patients treated with cladribine tablets 3.5 mg/kg and 3 in patients treated with placebo.
- To compare malignancy risk between treatment with cladribine tablets 3.5 mg/kg and placebo, incidence rates difference (RD) and incidence rate ratios (RR) were calculated (**Table 3**).
- The confidence intervals (CIs) for the RD included 0, and the CIs for the RR included 1 demonstrating that there was no statistically significant difference in malignancy risk between cladribine tablets 3.5 mg/kg and placebo.

Table 3. Incidence Rates, Risk Difference and Risk Ratio for Malignancies in Patients Treated with Cladribine Tablets 3.5 mg/kg or Placebo in the Monotherapy Oral Cohort

	Placebo (n = 641)	Cladribine tablets 3.5 mg/kg (n = 923)
Patients with events/Patient years at risk	3/2022.11	10/3414.20
Incidence per 100 PY	0.14836	0.29289
95% CI of incidence*	0.0478–0.4600	0.1576–0.5444
Risk Difference per 100 PY		0.1445
95% CI of Risk Difference per 100 PY†		-0.1656–0.4141
Risk Ratio		1.9742
95% CI of Risk Ratio‡		0.5433–7.1733

CI, confidence interval; **PY**, patient year.
* CI computed with the exact Clopper-Pearson formula.
† CI computed using the Miettinen and Nurminen method.
‡ CI computed with the Wald method for the number of subjects with events using a Poisson regression model with fixed effect for treatment group and log of time at risk as an offset.

Comparison With External Reference Populations

- Standardized incidence ratios (SIR) for malignancies were calculated in relation to the GLOBOCAN 2012 reference population with matched follow-up distribution (with respect to sex, age, and country).[4]
- Analysis of the malignancy SIR showed that the rate of malignancies with cladribine 3.5 mg/kg was almost identical (0.97, 95% CI 0.44–1.85) to the GLOBOCAN matched reference population.
- However, the SIR for the placebo group was numerically lower (0.48, 95% CI 0.14–1.53) than the matched reference population. This was in line with the findings of the analysis by Pakpoor *et al*. indicating that the low number of malignancy events seen with placebo in the CLARITY study was an unexpected outcome.
- The GLOBOCAN database does not include data on non-melanoma skin cancers (NMSCs). Therefore, an epidemiological database from Denmark, a country with low NMSC incidence rates, was used for comparison.[5]

Types of Malignancies

- There were no cases of hematological or lymphoproliferative cancers (**Table 4**). There was no clustering of specific tumor types, and the incidence of skin cancer was not increased after treatment with cladribine tablets 3.5 mg/kg compared with placebo.

Table 4. Type of Malignancies or Unspecified Tumors Reported in the Monotherapy Oral Cohort

SOC: malignancy or unspecified tumours*	Placebo (n = 3)	Cladribine tablets 3.5 mg/kg (n = 10)
Basal cell carcinoma	1	1
Bile duct adenocarcinoma	0	1
Breast cancer	0	1
Cervix carcinoma stage 0	2	0
Malignant melanoma	0	2
Ovarian cancer	0	1
Pancreatic carcinoma	0	1
Papillary thyroid cancer	0	1
Rectal cancer	0	1
Squamous cell carcinoma of skin	0	1

* Malignant or unspecified tumours determined by external adjudication.
SOC, System organ class.

Risk of Malignancies Over Time

- To further investigate any possible association between malignancies and exposure to cladribine tablets, the occurrence of malignancies over time was assessed.
- The malignancy rate for cladribine tablets 3.5 kg/mg during Years 1–4 was very close to the rate during Years 5-8+, indicating that the malignancy rate was constant during these 2 periods (**Table 5**).
- In contrast, the malignancy rate in the placebo group was higher after Year 4 than during Years 1–4, supporting the view that the low rate of events in this group during the earlier period was unexpected and probably due to chance.

Table 5. Adjusted Number of Malignancies per 100 Patient Years for Years 1–4 and Afterwards

	Cladribine tablets 3.5 mg/kg			Placebo		
	Patients with events	Time at risk (years)	Adjusted AESI per 100 PY	Patients with events	Time at risk (years)	Adjusted AESI per 100 PY
Years 1–4	8	2715.45	0.29	1	1689.99	0.059
Years 5-8+	2	711.84	0.28	2	334.59	0.598

AESI, adverse event of special interest; **PY**, patient year.

Malignancy Risk in a Larger Patient Cohort

- Safety data are also available for patients with MS from a study that involved treatment with cladribine tablets plus interferon (ONWARD), and 5 studies that involved the use of parenteral cladribine. This increases the patient cohort size for assessment of malignancy risk.
- The all exposed cohort included 1976 patients treated with cladribine (8650 patient years of exposure), and 802 placebo recipients (2631 patient years of exposure).
- Exposure to cladribine in the all exposed cohort, especially with regard to duration of follow up, was higher than exposure to placebo because the majority of clinical studies involved randomization of patients to treatment in a 2:1 ratio (active treatment:placebo).

Table 6. Incidence Rates, Risk Difference and Risk Ratio for Malignancies in Patients Treated with Cladribine or Placebo in the All Exposed Cohort

	Placebo (n = 802)	Cladribine tablets 3.5 mg/kg (n = 1976)
Patients with events/ Patient years at risk	4/2357.09	32/8579.39
Incidence per 100 PY	0.16970	0.37299
95% CI of incidence*	0.0637–0.4522	0.2638–0.5274
Risk Difference per 100 PY		0.2033
95% CI of Risk Difference per 100 PY†		-0.0785–0.3947
Risk Ratio		2.1979
95% CI of Risk Ratio‡		0.7773–6.2148

CI, confidence interval; **PY**, patient year.
* CI computed with the exact Clopper-Pearson formula.
† CI computed using the Miettinen and Nurminen method.
‡ CI computed with the Wald method for the number of subjects with events using a Poisson regression model with fixed effect for treatment group and log of time at risk as an offset.

- In the all exposed cohort, the CIs for the RD and RR included 0 and 1, respectively, demonstrating no statistically significant difference in malignancy risk between cladribine and placebo (**Table 6**).
- Analysis of the malignancy SIR showed that the rate of malignancies compared to the GLOBOCAN matched reference population was similar with cladribine (1.06, 95% CI 0.70–1.55), but numerically lower with placebo (0.38, 95% CI 0.11–1.21).
- In the all exposed cohort, the malignancy rate for cladribine during Years 1–4 (0.38) was identical to the rate during Years 5-8+, demonstrating that the malignancy rate remained constant over time. But, in the placebo group, the malignancy rate in Years 1–4 was 0.10 and during Years 5-8+ it was 0.57.

CONCLUSIONS

- **Analysis of malignancy rates in the overall clinical program of cladribine in multiple sclerosis does not show conclusive evidence of an increase compared to placebo-treated patients, either in the all exposed cohort or the monotherapy oral cohort.**
- **With regard to epidemiological analyses, the standardized incidence rate of malignancies with cladribine approached unity, indicating no increase in the incidence of malignancies in the clinical program compared with matched reference populations. The standardized incidence rate of malignancies in the placebo group was lower than expected from epidemiological databases.**
- **The malignancies observed in the cladribine program were typical of those seen in the general population with no increase in the types of cancer seen in immunosuppression.**
- **There was no increase in the incidence of malignancies over time in cladribine-treated patients.**

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DISCLOSURES

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