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Incidence Rate of Malignancies in People With Multiple Sclerosis Newly Initiating Cladribine Tablets or Fingolimod: Second Interim Results From CLARION

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RESEARCH IN CONTEXT

1. **These results support ongoing cladribine tablets safety data, which have shown no malignancy clustering or increased risk of malignancy.**
2. **There were few cases of malignancy in the cladribine tablets and fingolimod cohorts; further follow-up is needed.**

OBJECTIVES

To characterise the incidence rate (IR) and incidence rate ratio (IRR) of malignancies in people with multiple sclerosis (PwMS) newly initiating cladribine tablets or fingolimod.

INTRODUCTION

Cladribine tablets are a short-course treatment for relapsing multiple sclerosis (MS), with long-term follow-up data available from clinical trials and real-world studies.[1,2] As of June 2025, an estimated 131,017 PwMS have received cladribine tablets with 367,021 patient-years of exposure since final approval in 2017.

CLARION (EU post-authorisation study [PAS] Register number, EUPAS 24484) is a long-term, prospective, observational study comparing adverse events of special interest for PwMS newly initiating cladribine tablets with those newly initiating fingolimod in routine clinical practice with planned follow-up for 10 years.[3,4]

This second interim analysis of the CLARION study examined malignancies in PwMS newly initiating treatment with cladribine tablets or fingolimod.

METHODS

- CLARION includes both secondary data sources and primary data collection.

Data sources included in this interim analysis

Secondary data sources:
- The Italian Multiple Sclerosis and Related Disorders Registry
- MSBase: Australia, Belgium, Canada, Croatia, Kuwait, Lebanon, the Netherlands, and Turkey
- The national healthcare and MS registers in Norway and Sweden
- The Swiss MS Cohort (Switzerland)
- United States Department of Defense

Primary data collection:
- Multiple Sclerosis Documentation System 3D: Germany

- PwMS were classified for their entire follow-up according to treatment received at cohort entry. PwMS were excluded if they had any malignancy prior to inclusion or had 0 days of follow-up. Only first events were considered, and follow-up time after the first event was censored.
- The IR for the first malignancy event was obtained per 1000 person-years. The corresponding 95% confidence interval (CI) was estimated using Poisson regression. The IR was also calculated for subgroups based on prior disease-modifying therapy (DMT) use.
- The IRR (95% CI) for cladribine tablets versus fingolimod was estimated based on Poisson regression. Due to sparse data, the IRRs were not adjusted for prognostic factors, such as age, sex, or duration of DMT use.

RESULTS

- For this interim analysis (cutoff date 01 April 2023), 4402 PwMS were included in the cladribine tablets cohort and 3120 PwMS in the fingolimod cohort (**Supplementary Table 1**).
  - PwMS with prior malignancies within the interim analysis cohort who were excluded from the malignancy analyses: cladribine tablets cohort, n=49; fingolimod cohort, n=17.

Duration of follow-up by cohort

Cladribine tablets cohort	Fingolimod cohort
Mean ± SD: 1.9 ± 1.2 years (maximum: 5.4 years)	Mean ± SD: 2.8 ± 1.3 years (maximum: 5.4 years)

SD, standard deviation

- Malignancies were not commonly observed in either cohort (**Figure 1**).
- The IRR of malignancy for the cladribine tablets cohort compared with the fingolimod cohort was 0.72 (95% CI: 0.44, 1.18).

Figure 1. No Meaningful Difference in Malignancy IR Was Apparent Between Cohorts

Cohort	Number at risk	Time at risk, PY	Number of malignancies	IR of malignancy per 1000 PY (95% CI)
Cladribine tablets	4353	8201	26	**3.17** (2.16, 4.66)
Fingolimod	3103	8611	38	**4.41** (3.21, 6.06)

CI, confidence interval; IR, incidence rate; PY, person-years

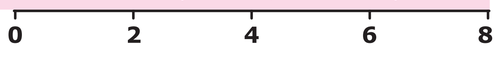
- Prior DMT use appeared to have no meaningful impact on risk of malignancy in both cohorts (**Figure 2**).
- Skin malignancies were the most-reported malignancy in both cohorts (**Table 1**).

Limitations

- Analyses adjusting for prognostic factors were not feasible due to sparse data.
- The difference in mean follow-up time could bias the comparison of IRs. As malignancy is expected to be mostly observed after multiple years of treatment initiation, and cladribine tablets users had a shorter mean follow-up time, they were less likely at risk of experiencing malignancy than the fingolimod users, which may have led to underestimation of the IR for this cohort.
- A potential selection bias, which for instance could be caused by different clinical practice (as an example, breast cancer screening before the start of cladribine tablets treatment), cannot be excluded.

Figure 2. Prior DMT Use Seems to Have No Meaningful Impact on Risk of Malignancy

Cohort	Prior DMT use	Number at risk	Number of malignancies	IR of malignancy per 1000 PY (95% CI)
Cladribine tablets	No prior DMT	1862	11	**2.95** (1.63, 5.33)
	Prior DMT	2491	15	**3.35** (2.02, 5.56)
Fingolimod	No prior DMT	1283	15	**4.66** (2.81, 7.73)
	Prior DMT	1820	23	**4.26** (2.83, 6.42)



CI, confidence interval; DMT, disease-modifying therapy; IR, incidence rate; PY, person-years

Table 1. Distribution of Malignancies During the Observation Period by Type and Cohort

Malignancy, n	Cladribine tablets N=4402	Fingolimod N=3120
Total first malignancy during observation period	26	38
Malignancies by primary site		
Skin	14	14
Melanoma of skin	0	5
Non-melanoma skin cancer	14	9
Breast	0	11
Male organs	2	4
Female genital organs	3	2
Colorectum and anus	2	2
Urinary tract	2	0
Trachea, bronchus, and lung	1	0
Lymphoid, haematopoietic, and related tissue	0	1
Other cancers	2	4
Brain and other parts of central nervous system, excluding endocrine tumours	0	1
Thyroid and other endocrine glands	2	1
Ill-defined, secondary, and unspecified sites or independent (primary) multiple sites	0	2

A potential selection bias, which for instance could be caused by different clinical practice (as an example, breast cancer screening before the start of cladribine tablets treatment), cannot be excluded.

CONCLUSIONS

- **In this second interim analysis, no meaningful difference in the IR of malignancy for the cladribine tablets cohort versus the fingolimod cohort was identified. However, the available follow-up time was limited, and malignancies were scarcely observed.**
- **The findings should be interpreted with caution because they were not adjusted for prognostic factors, and there was a longer follow-up time in the fingolimod cohort than in the cladribine tablets cohort.**
- **CLARION will provide long-term data that could further support treatment decisions of neurologists and PwMS.**

SCAN FOR AFFILIATIONS, DISCLOSURES, AND SUPPLEMENTARY MATERIALS

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Supplementary Materials

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Supplementary Table 1. Participant Demographics and Characteristics

	Cladribine tablets N=4402	Fingolimod N=3120
Female, n (%)	3178 (72.2)	2108 (67.6)
Age at inclusion, years, mean ± SD	39.4 ± 11.6	40.3 ± 11.3
Time since diagnosis of MS, years, mean ± SD	5.9 ± 6.8	6.6 ± 6.8
Number of relapses within 1 year prior to inclusion, n (%)		
0	2295 (52.1)	1766 (56.6)
1	1458 (33.1)	964 (30.9)
≥2	453 (10.3)	249 (8.0)
Unknown	196 (4.5)	141 (4.5)
EDSS at inclusion		
Median score category	>1.5 and ≤2.5	>1.5 and ≤2.5
Range (minimum, maximum)	(0.0, 8.0)	(0.0, 8.5)
Number of previous DMTs, n (%)		
0	1887 (42.9)	1288 (41.3)
1	1423 (32.3)	1047 (33.6)
≥2	1092 (24.8)	785 (25.2)
Malignancy prior to inclusion, n (%)	49 (1.1)	17 (0.5)

DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; SD, standard deviation