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The CLARION study: first report on safety findings in patients newly initiating treatment with cladribine tablets or fingolimod for multiple sclerosis

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ABSTRACT

Objectives: As part of the CLARION study: (1) characterize the incidence of severe infections, herpes zoster, and malignancies in patients newly initiating cladribine or fingolimod for relapsing multiple sclerosis (MS); (2) estimate the incidence of severe lymphopenia among cladribine users; and (3) describe prior/subsequent disease-modifying therapy (DMT) in both cohorts.

Methods: Patients were identified from seven participating MS registries/data sources. The incidence rate (IR) of each outcome per 1000 patient-years and its 95% confidence interval (95%CI) were estimated for cohorts using Poisson regression.

Results: By cut-off date (01-April-2020), 742 cladribine and 867 fingolimod users were included. Mean follow-up was ~1 year. The IR for severe infections from all contributing sources (except Denmark) was: cladribine, 7.37 (2.76,19.6); fingolimod, 6.55 (2.46,17.4). The corresponding IR for herpes zoster was 5.51 (1.78,17.1) and 3.27 (0.82,13.1), respectively, while values for opportunistic infections were 0 (0,6.76) and 1.63 (0.23,11.6), respectively. There were no events of progressive multifocal leukoencephalopathy in either cohort. The IR of severe lymphopenia was 63.9 (40.7,100.1) in 349 cladribine users from contributing sources. The IR of malignancies (cut-off date 01-April-2022) was 3.55 (1.59,7.90) for the cladribine cohort ($n = 1035$) and 3.55 (1.48,8.52) for the fingolimod cohort ($n = 843$) from three MS registries/data sources. In the combined data sources, 36.8% of cladribine and 27.4% of fingolimod users were DMT-naïve; after initiation of study treatment, 2.5% and 20.2% switched to another DMT, respectively.

Conclusion: No new safety signal was observed in patients treated with cladribine tablets, although results are limited by a relatively short duration of follow-up.

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Cladribine tablets; relapsing multiple sclerosis; safety; fingolimod

Introduction

Cladribine tablets[i] are a disease-modifying therapy (DMT) approved for the treatment of patients with relapsing multiple sclerosis (MS). Placebo-controlled studies completed in the clinical development program demonstrate decreased risk of relapse, disability progression, and magnetic resonance imaging (MRI) disease activity[1–4]. The mechanism of action of this short-course oral therapy for relapsing MS involves selective, transient reduction of lymphocyte counts[5–7] accompanied by clinical benefits that are sustained beyond recovery of total lymphocyte count – first demonstrated in the pivotal CLARITY and CLARITY Extension studies[1,2] and most recently in the MAGNIFY-MS study[8].

Because treatment with cladribine affects the immune system, severe infections and opportunistic infections (including progressive multifocal leukoencephalopathy [PML]) have been identified as important potential risks while re-activation of herpes zoster and tuberculosis (TB) are important

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identified risks. Safety data from the clinical development program show that, apart from herpes zoster, there was no increased risk of infections (including severe infections, opportunistic infections, or PML in patients treated with cladribine for MS[9,10]. As of July 2021, a total of 49,783.5 patient-years (PY) of exposure to cladribine have accrued from an estimated 35,668 patients who have received treatment post-approval[11]. Analysis and further real-life studies have shown that the safety profile of cladribine in clinical practice is consistent with that described in the clinical development program[11–13]. In view of its mechanism of action and prolonged duration of effect, it is important to understand the longer-term safety of such DMTs in routine clinical practice[14–16]. Long-term observation in a large cohort of patients newly exposed to cladribine compared with relevant comparator drugs is required to definitively assess if cladribine exposure is associated with an increased risk of malignancy.

It is against this background that the CLARION study, which meets the requirements requested by regulatory authorities for post-approval safety studies, is collecting additional real-life and longer-term safety data for adverse events of special interest (AESI) with cladribine[17]. CLARION will ultimately involve 8000 patients newly initiating cladribine or fingolimod (4000 patients per cohort), included over a 5-year timeframe and followed for between 10 and 15 years. Fingolimod, a sphingosine-1-phosphate receptor modulator that sequesters lymphocytes in lymph nodes, was selected as the primary comparator for this study given that both agents have a similar indication and are orally administered[17].

In this article, we provide the results of the CLARION first interim analysis with a cut-off date of 01-April-2020 and of the first analysis of malignancies with a cut-off date of 01-April-2022. The specific objectives of this analysis were to: (1) characterize the incidence of severe infections, herpes zoster, TB, PML, other opportunistic infections, and malignancies in patients with relapsing MS newly initiating oral treatment with cladribine or fingolimod[ii]; (2) estimate the incidence of severe lymphopenia among those treated with cladribine; and (3) describe prior and subsequent use of DMTs in these cohorts.

Materials and methods

Study design and population

CLARION (EUPAS24484) is a multi-country, multicenter, long-term, comparative, non-interventional cohort study. MS patients newly initiating oral treatment with cladribine or fingolimod, after the country-specific launch date for cladribine tablets were identified from seven participating MS registries/data sources (Danish, Finnish, Norwegian, and Swedish MS registries; MSBase [multiple countries]; Multiple Sclerosis Documentation System 3D [MSDS3D; Germany]; and the Swiss MS Cohort [SMSC]).

The study overall is enrolling patients newly initiating cladribine or fingolimod for relapsing MS ($n = 4000$ each). Patients who had received fingolimod before newly initiating cladribine, or cladribine before newly initiating fingolimod, were not eligible for the study. Full details of the study methods are published elsewhere[17].

Outcomes

Outcomes were severe infections (except TB, PML, and opportunistic infections), herpes zoster regardless of severity, TB, PML, opportunistic infections (including, but not limited to, candidiasis [of bronchi, trachea, esophagus, or lungs], cytomegalovirus diseases, infective encephalopathy, histoplasmosis, *Mycobacterium avium complex* [MAC], recurrent pneumonia, and toxoplasmosis of the brain) and malignancies (all and by type). Four sources contributed data on severe lymphopenia (grade $\geq$3), which was recorded based on laboratory test results with lymphocyte count $<0.5 \times 10^9$/L (Finnish MS Registry, MSBase, MSDS3D, and the SMSC). In Germany, additional information on severe lymphopenia, reported as an adverse event, was available. Any subsequent DMT use was defined as the first subsequent DMT after initiation of study treatment.

Definition of exposure

The following definitions of exposure were used (examples of how the definitions were applied for selected scenarios are shown in Supplementary Figure S1). For the *intention-to-treat* (ITT) exposure definition, patients were classified according to treatment received at cohort entry (inclusion). For the *as-treated* definition, exposure is time-dependent, and patients were classified per on-going treatment at a given time (current exposure to cladribine; current exposure to fingolimod; or no current exposure to study treatment). At treatment discontinuation or switch from initial study treatment to another study treatment or to any other DMT, current exposure is extended by a washout period of 6 months (+6-month latency as-treated exposure definition) or 12 months (+12-month latency as-treated exposure definition) for the discontinued treatment after which the exposure to the newly initiated treatment is started. For the *on-treatment* exposure definition, patients were classified according to treatment received at cohort entry; follow-up time is censored 6 months after treatment discontinuation (+6-month latency on-treatment exposure definition) or 12 months after treatment discontinuation (+12-month latency on-treatment exposure definition).

Statistical analyses

All outcomes (except severe lymphopenia) were analyzed using the ITT exposure definition, and corresponding sensitivity analyses were performed using the +6- and +12-month latency as-treated and on-treatment exposure definitions. For severe lymphopenia, the main analysis used the +6-month latency as-treated exposure definition. Sensitivity analyses were also performed using a + 12-month latency as-treated exposure definition.

Using the ITT exposure definition, the incident rates (IRs) of malignancy events were analyzed in two ways: main

analysis included only patients who had no prior history of malignancy; and sensitivity analysis including all patients regardless of having known prior malignancy or not. For the main analysis, analysis by malignancy type was also performed.

For purposes of analysis, patient time-at-risk was counted from cohort entry to the earliest date of first event, last visit date, or cut-off date (01-April-2020 for infections and 01-April-2022 for malignancies). The malignancies cut-off date was extended to 2022 to allow for a longer follow-up time. IRs per 1000 PY and corresponding 95% confidence intervals (CIs) were estimated for each cohort using interval-censored Poisson regression[18]; for IRs of zero, the 95% CI was estimated using the exact method[19]. CIs for the difference between IRs were calculated based on Miettinen and Nurminen[20].

Prior DMT use was described by cohort and type and included number of prior DMTs used, any prior, last prior, and second-to-last DMT used before study treatment. Subsequent DMT use after initiating treatment with cladribine or fingolimod was also described. Results are presented for DMTs with at least 10% of the DMT use in cladribine or fingolimod cohorts (all MS data sources combined, excluding the Danish MS Registry). In Denmark, numbers and percentages were sometimes provided as ranges due to restrictions of reporting small observations. Overall reports of demographic and previous treatment data presented below therefore exclude the Danish MS Registry data, which are reported separately.

Concerning severe lymphopenia, due to uncertainties on the definitions and coverage for severe lymphopenia in Sweden and Norway, these data sources were also excluded from the assessment. Data concerning severe lymphopenia are not available in the included Danish MS registries.

Ethics approval

The CLARION study is conducted according to Guidelines for Good Pharmacoepidemiology Practice (GPP) and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Code of Conduct, which ensures compliance with General Data Protection Regulation (GDPR). The study protocol was approved in Germany by the Ethikkommission of the Technische Universität Dresden (reference number: EK 338092018), in Switzerland by the Ethikkommission Nordwest- und Zentralschweiz (EKNZ) (reference number: 2019-01949), and in Norway by the Regional Committee for Medical and Health Research Ethics (reference number: 2018/2530). Data permits are granted by approval bodies in each Nordic country.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Results

For this first interim analysis, with a cut-off date of 01-April-2020, data from 1958 patients initiating treatment with cladribine or fingolimod were considered for inclusion. After exclusion of patients not fulfilling the inclusion criteria, there were 742 eligible patients in the cladribine cohort and 867 patients in the fingolimod cohort (Supplementary Figure S2 and Table 1). For all MS data sources combined (excluding the Danish MS Registry), the cladribine cohort ($n = 606$) had a mean age of 41.0 (SD ± 12.6) years compared to 40.0 (SD ± 11.0) years for the fingolimod cohort ($n = 475$). The proportion of female patients was 74.1% and 69.7%, respectively, while patients had a mean follow-up time since treatment initiation of 0.9 (SD ± 0.5) years and 1.3 (SD ± 0.7) years. In the cladribine cohort the mean duration of MS since diagnosis was 6.7 years (SD ± 7.7), the mean Expanded Disability Status Scale (EDSS) score closest to inclusion was 2.5 (SD ± 2.0), and the mean number of relapses within 1 year prior to inclusion was 0.6 (SD ± 0.8). In the fingolimod cohort, mean duration of MS was 6.0 years (SD ± 6.7), mean EDSS score was 2.0 (SD ± 1.5), and mean number of relapses in the prior year was 0.7 (SD ± 0.8). Patient demographics and baseline disease characteristics in the Danish MS Registry cohort were similar to other MS registry patients (Table 1).

Incidence of infections

The IR of infections using the ITT exposure definition is shown in Table 2. Considering severe infections for all MS data sources combined (excluding the Danish MS Registry), the IR per 1000 PY (95% CI) was 7.37 (2.76, 19.6) for the cladribine cohort and 6.55 (2.46, 17.4) for the fingolimod cohort. The corresponding IR per 1000 PY (95% CI) for herpes zoster was 5.51 (1.78, 17.1) and 3.27 (0.82, 13.1), respectively. For opportunistic infections, the IR per 1000 PY (95% CI) was 0 (0, 6.76) in the cladribine cohort and 1.63 (0.23, 11.6) in the fingolimod cohort. No recurrent events were observed during the follow-up period, and there were no events of PML recorded in either cohort. In the Danish MS Registry, there were 1–4 TB events in the fingolimod cohort, with an IR per 1000 PY (95% CI) of 3.50 (0.58, 21.2) and none in the cladribine cohort.

Similar results were obtained using sensitivity analyses with +6-month latency and +12-month latency as-treated definitions and the on-treatment definitions (Supplementary Tables S1 and S2).

Incidence of all malignancies

For the first malignancy analysis, with a cut-off date of 01-April-2022, data from 1913 patients (1058 cladribine and 855 fingolimod users) were considered for inclusion from the three MS data sources with relevant data: MSBase, MSDS3D, and SMSC. Of these, 35 patients (23 cladribine and 12 fingolimod users) were excluded from the main analysis due to presence of known malignancy prior to study drug initiation. Thus, 1035 patients in the cladribine cohort and 843 patients in the fingolimod cohort were included in the main analysis (i.e. patients without known prior malignancy). The mean follow-up time since treatment initiation was 1.6 (SD ± 1.1)

Table 1. Patient demographics and baseline disease characteristics.

	All MS data sources, excluding Danish MS Registry[1]		Danish MS Registry	
	Cladribine cohort $n = 606$	Fingolimod cohort $n = 475$	Cladribine cohort $n = 136$	Fingolimod cohort $n = 392$
Age at inclusion, years				
Mean (SD)	41.0 (12.6)	40.0 (11.0)	40.6 (10.8)	40.0 (11.2)
Range (min, max)	(19.0, 76.0)	(16.0, 78.0)	NR	NR
Female, n (%)	449 (74.1)	331 (69.7)	82 (60.3)	262 (66.8)
Duration of follow-up at the time of data cut-off, years				
Mean (SD)	0.9 (0.5)	1.3 (0.7)	1.0 (0.6)	1.6 (0.7)
Range (min, max)	(0.0, 2.3)	(0.0, 2.5)	NR	NR
Patient-years	545.5	613.1	142.1	633.5
Mean time since MS diagnosis at inclusion, years (SD)	6.7 (7.7)	6.0 (6.7)	6.4 (6.9)	6.5 (6.8)
EDSS score closest to inclusion, mean (SD)	2.5 (2.0)	2.0 (1.5)	2.4 (1.7)	2.4 (1.5)
Number of relapses within 1 year prior to inclusion				
Mean (SD)	0.6 (0.8)	0.7 (0.8)	0.7 (0.8)	0.6 (0.8)
Median (Q1, Q3)	0 (0, 1)	0 (0, 1)	0.0 (0, 1)	0 (0, 1)
Data source, n				
Finnish MS Registry	73	123	–	–
MSBase	132	49	–	–
MSDS3D	130	104	–	–
Norwegian MS Registry and Biobank	183	136	–	–
Swedish MS Registry	80	50	–	–
Swiss MS Cohort	8	13	–	–
Danish MS Registry	–	–	136	392

Abbreviations. EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; MSDS3D, Multiple Sclerosis Documentation System 3D; NR, not reported; SD, standard deviation.
[1]Patients from the Danish MS Registry were excluded from the 'All MS data sources' group and are reported separately, due to restrictions of reporting small number of observations (<5).

Table 2. Incidence rate of infections per 1000 patient-years: ITT exposure definition.

	Number of events	Total time at risk (PY)	IR (95% CI)	Number of events	Total time at risk (PY)	IR (95% CI)	IR difference (95% CI)
All MS data sources, excluding the Danish MS Registry[1]							
	Cladribine cohort $n = 606$			**Fingolimod cohort $n = 475$**			
Severe infections[2]	4	543	7.37 (2.76, 19.6)	4	611	6.55 (2.46, 17.4)	0.82 (−10.30, 13.0)
Herpes zoster	3	544	5.51 (1.78, 17.1)	2	611	3.27 (0.82, 13.1)	2.24 (−6.98, 13.1)
Opportunistic infections	0	546	0 (0, 6.76)	1	612	1.63 (0.23, 11.6)	−1.63 (−9.20, 5.37)
Danish MS Registry							
	Cladribine cohort $n = 136$			**Fingolimod cohort $n = 392$**			
Severe infections[3]	0	142	0 (0, 25.9)	8	622	12.9 (6.43, 25.7)	−12.9 (−25.2, 13.5)
Herpes zoster	0	142	0 (0, 25.9)	[1–4]	632	3.50 (0.58, 21.2)	−3.50 (NE)
Tuberculosis	0	142	0 (0, 25.9)	[1–4]	632	3.50 (0.58, 21.2)	−3.50 (NE)

Abbreviations. CI, confidence interval; IR, incidence rate; ITT, intention-to-treat; MS, multiple sclerosis; NE: not estimated; PY, patient-years.
[1]Patients from the Danish MS Registry were excluded from the 'All MS data sources' group and are reported separately, due to restrictions of reporting small number of observations (<5).
[2]Excluding tuberculosis, progressive multifocal leukoencephalopathy, and other opportunistic infections.
[3]Excluding progressive multifocal leukoencephalopathy and other opportunistic infections.
CIs of incidence rates were estimated for each cohort using interval-censored Poisson regression. For incidence rates of zero, the 95% CI was estimated using the exact method.

years and 1.7 (SD ± 1.0) years, respectively, for the cladribine and fingolimod cohorts.

The IR of malignancies using the ITT exposure definition is shown in Table 3. In the main analysis, for all malignancies, (excluding patients with known prior malignancy), the IR per 1000 PY (95% CI) was 3.55 (1.59, 7.90) for the cladribine cohort and 3.55 (1.48, 8.52) for the fingolimod cohort. The number of patients with malignancies (without prior known malignancy), according to type of malignancy and cohort using the ITT exposure definition is shown in Table 4. In the cladribine cohort, 1 colon cancer, 2 breast cancers, 2 cervical cancers, and 1 renal cancer were reported. In the fingolimod cohort, 1 non-melanoma skin cancer, 1 breast cancer, 1 cervical cancer, 1 testicular cancer (seminoma), and 1 cancer classified as ill-defined, secondary and unspecified sites or independent (primary) multiple sites were reported.

The IR of malignancies by cohort in all patients regardless of prior history of malignancy is presented in Table 3. In this sensitivity analysis, the IR per 1000 PY (95% CI) was 3.47 (1.56, 7.72) for the cladribine cohort and 3.49 (1.45, 8.38) for the fingolimod cohort. These results are consistent with the results of the main analysis.

Incidence of severe lymphopenia

The IR of severe lymphopenia in the cladribine cohort (using the +6-month latency as-treated definition, for contributing

Table 3. Incidence rate of malignancies (all) per 1000 patient-years: ITT exposure definition[1].

	Main analysis (patients without known prior malignancy)		Sensitivity analysis (including patients with any history of prior malignancy)	
	Cladribine cohort	Fingolimod cohort	Cladribine cohort	Fingolimod cohort
Total number of patients at risk	1035	843	1058	855
Number of first events	6	5	6	5
Total time at risk (PY)	1690	1409	1731	1434
IR (95% CI)	3.55 (1.59, 7.90)	3.55 (1.48, 8.52)	3.47 (1.56, 7.72)	3.49 (1.45, 8.38)
IR difference (95% CI)	0.00 (−5.10, 4.66)		−0.02 (−5.03, 4.53)	

Abbreviations. CI, confidence internal; IR, incidence rate; IR difference, cladribine minus fingolimod (i.e. IR difference for cladribine cohort relative to fingolimod cohort); ITT, intention-to-treat; MS, multiple sclerosis; MSDS3D, Multiple Sclerosis Documentation System 3D; PY, patient-years.
[1]Patients from MSBase, MSDS3D, and the Swiss MS Cohort are included in the analysis (cut-off date: 01-April-2022).

Table 4. Incidence rate of malignancy per 1000 patient-years by malignancy type and cohort: ITT exposure definition (patients without known prior known malignancy)[1].

Type	Cladribine cohort $n = 1035$			Fingolimod cohort $n = 843$		
	Patients	Events	IR (95% CI)	Patients	Events	IR (95% CI)
Colon	1	1	0.59 (0.08, 4.19)	0	0	0.00 (0.00, 2.61)
Non-melanoma skin cancer	0	0	0.00 (0.00, 2.18)	1	1	0.71 (0.10, 5.02)
Breast (in women)	2	2	1.18 (0.30, 4.72)	1	1	0.71 (0.10, 5.02)
Cervical	2	2	1.18 (0.30, 4.72)	1	1	0.71 (0.10, 5.02)
Testicular	0	0	0.00 (0.00, 2.18)	1	1	0.71 (0.10, 5.02)
Kidney and renal pelvis	1	1	0.59 (0.08, 4.19)	0	0	0.00 (0.00, 2.61)
Ill-defined, secondary and unspecified sites or independent (primary) multiple sites	0	0	0.00 (0.00, 2.18)	1	1	0.71 (0.10, 5.02)

Abbreviations. CI, confidence internal; IR, incidence rate; ITT, intention-to-treat; MS, multiple sclerosis; MSDS3D, Multiple Sclerosis Documentation System 3D.
[1]Patients from MSBase, MSDS3D, and the Swiss MS Cohort are included in the analysis (cut-off date: 01-April-2022).

Table 5. Incidence rate of severe lymphopenia per 1000 patient-years in the cladribine cohort[1].

Definition of exposure	Number of patients	Number of (first) events	Total time at risk (PY)	IR (95% CI)
+6-month latency as-treated	349	19	298	63.9 (40.7, 100.1)
+12-month latency as-treated (sensitivity analysis)	346	19	297	64.0 (40.8, 100.3)

Abbreviations. CI, confidence interval; IR, incidence rate; MS, multiple sclerosis; MSDS3D, Multiple Sclerosis Documentation System 3D; PY, patient-years.
[1]Patients from the Finnish MS Registry, MSBase, MSDS3D, and the Swiss MS Cohort are included in the analysis.
CIs of incidence rates were estimated using interval-censored Poisson regression.

data sources) is shown in Table 5. For contributing data sources, there were 19 events of severe lymphopenia with an IR per 1000 PY (95% CI) of 63.9 (40.7, 100.1). No recurrent events were observed. Similar results were obtained using the +12-month latency as-treated definition in sensitivity analysis (Table 5).

History of DMT use

Any prior use of DMT before study treatment is shown in Table 6. For all MS data sources combined (excluding the Danish MS Registry), 63.2% of the cladribine cohort and 72.6% of the fingolimod cohort had at least one prior DMT use over the years before initiation of study treatment. Most patients had used only one prior DMT (31.8% in the cladribine cohort and 35.4% in the fingolimod cohort). Interferon beta-1a, dimethyl fumarate, and glatiramer acetate were the most common treatments among prior DMT users in both cohorts.

For the Danish MS Registry, 81.6% of patients in the cladribine cohort and 86.2% of the fingolimod cohort used at least one prior DMT, and most had used only one prior DMT (28.7% and 43.1%, respectively). Teriflunomide and interferon beta-1a were the most common treatments among prior DMT users in both cohorts.

Last/second-to-last DMT before study treatment

Supplementary Table S3 summarizes the findings for last and second-to-last DMT before study treatment. For all MS data sources combined (excluding the Danish MS Registry), the most common DMT used immediately (last) before cladribine or fingolimod was teriflunomide, while interferon beta-1a was the most common second-to-last DMT used. For the Danish MS Registry, the most common DMTs used immediately (last) before cladribine or fingolimod were natalizumab and teriflunomide, respectively, while interferon beta-1a was the most common second-to-last DMT used.

Subsequent DMT use

Subsequent DMT use among the two cohorts is shown in Supplementary Table S4. For all MS data sources combined (excluding the Danish MS Registry), 20.2% of patients in the fingolimod cohort used a subsequent DMT during the mean 1.3 years' follow-up; the corresponding value for the cladribine cohort was 2.5% over 0.9 years. Switching to natalizumab (46.7%) or rituximab (33.3%) were the most frequent approaches in the cladribine cohort, while rituximab (35.4%) and cladribine (18.8%) were most often used following fingolimod. Similar findings were observed for patients in the Danish MS Registry, with 25.5% of the

Table 6. History of prior DMT use before initiation of study treatment.

	All MS data sources, excluding Danish MS Registry[1]		Danish MS Registry	
	Cladribine cohort $n = 606$	Fingolimod cohort $n = 475$	Cladribine cohort $n = 136$	Fingolimod cohort $n = 392$
Any prior DMT use for MS, n (%)				
No DMT	223 (36.8)	130 (27.4)	25 (18.4)	54 (13.8)
One DMT	193 (31.8)	168 (35.4)	39 (28.7)	169 (43.1)
Two DMTs	104 (17.2)	113 (23.8)	38 (27.9)	121 (30.9)
Three or more DMTs	86 (14.2)	64 (13.5)	34 (25.0)	48 (12.2)
Any prior DMT use by type, n (%)	**383 (63.2)**	**345 (72.6)**	**111 (81.6)**	**338 (86.2)**
Dimethyl fumarate[2]	135 (35.2)	116 (33.6)	36 (32.4)	56 (16.6)
Interferon beta-1a[2]	130 (33.9)	152 (44.1)	50 (45.0)	172 (50.9)
Glatiramer acetate[2]	128 (33.4)	112 (32.5)	32 (28.8)	49 (14.5)
Teriflunomide[2]	110 (28.7)	106 (30.7)	47 (42.3)	173 (51.2)
Natalizumab[2]	79 (20.6)	48 (13.9)	47 (42.3)	94 (27.8)
Interferon beta-1b[2]	50 (13.1)	54 (15.7)	5 (4.5)	16 (4.7)

Abbreviations. DMT, disease-modifying therapy; MS, multiple sclerosis.
[1]Patients from the Danish MS Registry were excluded from the 'All MS data sources' group and are reported separately, due to restrictions of reporting small observations (<5).
[2]Among patients with prior DMT use.
Only DMTs used by 10% or more of patients in at least one cohort are included in the table.

fingolimod cohort using a subsequent DMT compared to 0.7–2.9% of patients in the cladribine cohort. Ocrelizumab was the most used therapy in patients treated with fingolimod who went on to use a subsequent DMT (used by 55.0% of this population).

Discussion

The reported results, from the first of four planned interim analyses of CLARION, planned with 3-year periodicity, and the first malignancy analysis, are based on 1606 patients mostly included from Denmark, Norway, Germany, and Australia (MSBase). No new safety signal in patients treated with cladribine has been identified in this interim analysis. Based on safety data from the clinical development program for cladribine as an oral therapy for MS[9,10], herpes zoster and TB have been defined by regulatory authorities as identified risks and other AESIs as potential risks. By providing information on AESI during longer-term follow-up in clinical practice, CLARION will provide data to guide treatment decision-making for patients with relapsing MS and further characterize the safety profile of cladribine in the real-world setting. As of 01-Nov-2022, a total of 5085 patients have been enrolled into the study (cladribine cohort, $n = 2956$; fingolimod cohort, $n = 2129$), which is 63.6% of the targeted study size.

MS registries and similar data sources have enhanced their data coverage and instituted collaborations to allow the conduct of post-approval safety studies such as CLARION. Such collaborations enable the link with national health registries in Nordic countries, which is an important strength of the CLARION study[17]. Moreover, data quality in CLARION is assessed through yearly assessment against pre-specified data quality indicators (DQIs). Each data source is responsible for the quality and integrity of collected study data and a set of DQIs has been developed to monitor the quality of study data in terms of consistency, accuracy, completeness, and representativeness.

It is important to consider the relatively short follow-up period at the time of data cut-off used for this analysis – around a year in both cohorts – so no statistical comparisons were made for the incidence of severe infections, herpes zoster, or opportunistic infections. There were no events of PML recorded in either cohort. It also has to be considered that, apart from MSDS3D (Germany; primary data collection[21]), data sources and registries do not provide details of the *type* of severe infection. This precludes an examination of some questions of clinical interest, such as whether severe infections occur in context of previous DMTs or simultaneously with lymphopenia.

Most patients used at least one prior DMT in both the cladribine and fingolimod cohorts. Interferon beta-1a, dimethyl fumarate, and glatiramer acetate were the most frequently used DMT (at any point) prior to study treatment, while teriflunomide, dimethyl fumarate, and natalizumab were the most common DMTs used immediately before study inclusion. Around one-third of patients included in CLARION were treatment-naïve. This treatment strategy, selected by physicians and observed in CLARION, is supported by increasing evidence that high-efficacy DMTs should be considered as the first DMT in the treatment sequence for many patients, i.e. at the start of their MS disease course to delay disease worsening and disability accumulation.

There were few instances of subsequent DMT use recorded in the cladribine cohort (2.5%). This result is consistent with other real-world studies that have shown low switch rates after initiation of cladribine[22–24], although the mean duration of follow-up for the present analysis was relatively short (0.9 years in the cladribine cohort and 1.3 years in the fingolimod cohort).

General limitations relating to the study design and data sources of CLARION have previously been described[17]. The study includes characterization of the incidence of severe lymphopenia in the cladribine cohort but not in the fingolimod cohort as an objective. This is due to the different medical practices used and the characterization of lymphopenia being conducted at different time points for the two DMTs[25]. It is therefore important to consider this when evaluating the benefit:risk of the treatments based on study results. In this first interim analysis, however, the patient number of events of severe lymphopenia and severe infections was too small to perform this analysis. Additionally, while data on human

papillomavirus (HPV) were collected as part of the protocol, the interim results are not reported in this publication as the data are limited and contain high proportions of missing data. The CLARION study population may represent patients with relapsing MS initiating cladribine or fingolimod treatment relatively early in their treatment course. Prior use of cladribine or fingolimod was an exclusion criterion to allow evaluation of the safety of the first treatment in the evaluated cohorts. In the source population considered for inclusion, 19.8% of cladribine users had previously been treated with fingolimod and were excluded from the study. However, the observed baseline characteristics and variation across the MS registries/data sources indicate that the CLARION study population, including the proportion of patients who were treatment naïve, is similar to what has been reported in the literature for the general MS population[26]. Due to the way the data are obtained in the CLARION study – based mainly on the secondary use of data – the capacity to study all cases of malignancy are limited, as too is the ability to collect risk factors with enough granularity to ascertain the risk factors for developing cancer in patients treated with cladribine or fingolimod. Further analyses to compare cancer/non-cancer patients warrants further analysis, but the follow-up period is too short in the current interim analysis. Finally, while not a limitation *per se* for this interim analysis, it is also important to consider that there was a relatively high frequency of treatment switches to rituximab, a high-efficacy drug that is not approved by the European Medicines Agency or the U.S. Food and Drug Administration for use in patients with MS. This may reflect the widespread use of rituximab for MS in clinical practice in Nordic countries[27–29], a region that contributed a major proportion of patients in the current analysis. For future analyses, with longer follow-up, the proportion of switchers to anti-CD20 agents may affect risk of infection and should be considered.

Conclusions

The results of the first interim report of the CLARION study confirms that it is possible to combine data from MS registries/data sources from several countries, leveraging primary and secondary data collection to offer a broad representation of patients with relapsing MS who are newly initiating oral treatment with cladribine or fingolimod. No new safety signal was observed in patients treated with cladribine, although results are limited by a relatively short duration of follow-up. CLARION will continue to monitor the safety profile of cladribine as planned, thereby providing longer-term safety data for neurologists and patients to assist treatment decision-making in the setting of relapsing MS.

Notes

i. Mavenclad
ii. Gilenya

Transparency

Declaration of funding

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Declaration of financial/other relationships

HB's institution (Monash University) received compensation for consulting, talks, and advisory/steering board activities from Alfred Health, Biogen, Merck, Novartis, Roche, and UCB; research support from Biogen, Merck, MS Research Australia, National Health and Medical Research (Australia), Medical Research Future Funds (Australia) Novartis, the Oxford Health Policy Forum, and Roche. He has received personal compensation for steering group activities from Oxford Health Policy Forum. **JH** has received honoraria for serving on advisory boards for Biogen, Novartis, and Sanofi, and speaker fees from Bayer, Biogen, Merck, Novartis, Sanofi, and Teva. He has served as Principal Investigator for projects, or received unrestricted research support from, Bayer, Biogen, Merck, Sanofi, and Teva. His MS research is funded by the Swedish Research Council and the Swedish Brain foundation. **MS-H** has served as an adviser or speaker for Biogen, Celgene (BMS), Novartis, Roche, Sanofi, and Teva; has received institutional research grants for clinical research from Bayer, Biogen, Merck, Novartis, and Roche; and support for congress participation from Biogen, Celgene (BMS), Novartis, Roche, Sanofi, and Teva. **TZ** has served as an advisor or consultant for Biogen, BMS, Merck, Novartis, Roche, Sanofi, Teva, and Viatris. Served as a speaker or a member of a speaker's bureau for Biogen, BMS, Merck, Novartis, Roche, Sanofi, and Teva. TZ has also received grants for clinical research from Biogen, Novartis, Roche, Sanofi, and Teva. **JK** has received speaker fees, research support, travel support, and/or served on advisory boards by Swiss MS Society, Swiss National Research Foundation (320030_189140/1), University of Basel, Progressive MS Alliance, Bayer, Biogen, Celgene (BMS), Merck, Novartis, Octave Bioscience, Roche, and Sanofi. **SW** has received honoraria for serving on advisory boards for Biogen, Janssen, and Sanofi, and speaker fees from Biogen, Janssen, and Sanofi. He has served as Principal Investigator for projects or received unrestricted research support from Biogen. **MM** has served on scientific advisory boards for AbbVie, Actelion (Janssen/J&J), Biogen, Merck, Novartis, Roche, and Sanofi; has received honoraria for lecturing from Biogen, Merck, Novartis, and Sanofi; and has received research support and support for congress participation from Biogen, Merck, Novartis, Roche, and Sanofi. **JRB** has received honoraria as a Scientific Advisory Board member for Inhibikase and Novartis; has received consultancy fees from Amgen, Celgene (BMS), Dr. Reddy's Laboratories, EMD Serono Research & Development Institute, Inc., Billerica, MA, USA, an affiliate of Merck KGaA, Encycle, Excision Bio, MAPI, Merck, Millennium/Takeda, Morphic, Sanofi, and Shire; and has received honoraria and institutional grants for consultancy from Biogen and Roche. **NM** has consulted with Merck. **AA** is a former employee of EMD Serono Research & Development Institute, Inc., Billerica, MA, USA, an affiliate of Merck KGaA. **IB** is an employee of IQVIA, a contract research organization that performs commissioned pharmacoepidemiological studies for several pharmaceutical companies. **MS** is an employee of Merck Healthcare KGaA, Darmstadt, Germany. A peer reviewer on this manuscript disclosed that they received travel funds for research meetings from Novartis. Peer reviewers on this manuscript have received an honorarium from CMRO for their review work but have no other relevant financial relationships to disclose.

Author contributions

HB, JH, MS-H, TZ, MM, JRB, NM, AA, IB, and MS were involved in the concept and design. All authors were involved in data interpretation, the drafting and revising of the article for intellectual content, and the final version to be published. All authors agree to be accountable for all aspects of the work.

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Data availability statement

Any requests for data by qualified scientific and medical researchers for legitimate research purposes will be subject to Merck's Data Sharing Policy. All requests should be submitted in writing to Merck's data sharing portal https://www.merckgroup.com/en/research/our-approach-to-research-and-development/healthcare/clinical-trials/commitment-responsible-data-sharing.html. When Merck has a co-research, co-development, or co-marketing or co-promotion agreement, or when the product has been out-licensed, the responsibility for disclosure might be dependent on the agreement between parties. Under these circumstances, Merck will endeavor to gain agreement to share data in response to requests.

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