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Safety of cladribine tablets in the treatment of patients with multiple sclerosis: An integrated analysis

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ABSTRACT

Background: Treating patients with relapsing multiple sclerosis (MS) with cladribine tablets (two times 4 or 5 days of treatment each year for 2 years) results in long-lasting efficacy, with continued stability in many patients for 4 or more years. Safety and tolerability outcomes from individual clinical studies with cladribine tablets have been reported previously.

Objective: Report safety data from an integrated analysis of clinical trials and follow-up in patients with MS to further characterize the safety profile of cladribine tablets.

Methods: Data for patients treated with cladribine tablets 10 mg (MAVENCLAD®; 3.5 mg/kg cumulative dose over 2 years, referred to as cladribine tablets 3.5 mg/kg) as monotherapy (n = 923) or placebo (n = 641) in Phase III clinical trials (CLARITY, CLARITY Extension and ORACLE-MS) and followed up in the PREMIERE registry were aggregated (Monotherapy Oral cohort). To better characterize rare events, additional data from earlier studies which involved the use of parenteral cladribine in patients with MS, and the ONWARD study, in which patients were given cladribine tablets in addition to interferon (IFN)-β or placebo plus IFN-β were included in an All Exposed cohort (cladribine, n = 1926; placebo, n = 802). Adjusted adverse events incidences per 100 patient-years (Adj-AE per 100 PY) were calculated for the integrated analyses.

Results: The incidence rate of treatment-emergent adverse events (TEAEs) in the Monotherapy Oral cohort was 103.29 vs. 94.26 Adj-AEs per 100 PY for placebo. TEAEs that occurred more frequently with cladribine tablets were mainly driven by the TEAEs of lymphopenia (Adj-AE per 100 PY 7.94 vs. 1.06 for placebo) and lymphocyte count decreased (Adj-AE per 100 PY 0.78 vs. 0.10 for placebo) as anticipated due to the mode of action of cladribine. An increase in TEAE incidence rate was also observed in the cladribine tablets 3.5 mg/kg group vs. placebo for herpes zoster (Adj-AE per 100 PY 0.83 vs. 0.20, respectively). There were no cases of systemic, serious disseminated herpes zoster attributed to treatment with cladribine tablets. In general there was no increase in the risk of infections including opportunistic infections with cladribine tablets versus placebo, except for herpes zoster. Periods of severe lymphopenia ($< 0.5 \times 10^9$ cells/L) were associated with an increased frequency of infections, but the nature of these was not different to that observed in the overall patient group treated with cladribine tablets 3.5 mg/kg. Within the constraints of a limited sample size, malignancy rates in the overall clinical program for cladribine in MS did not show evidence of an increase compared to placebo-treated patients and there was no increase in the incidence of malignancies over time in cladribine-treated patients.

Conclusion: The AE profile for cladribine tablets 3.5 mg/kg as a monotherapy has been well-characterized in a pooled population of patients from early to more advanced relapsing MS. There was no increased risk for infections in general except for a higher incidence of herpes zoster. Lymphopenia was amongst the most frequently

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observed TEAEs that occurred at a higher incidence with cladribine relative to placebo. There was also no increase in malignancy rates for cladribine relative to placebo.

1. Introduction

Cladribine tablets 10 mg (MAVENCLAD®; 3.5 mg/kg cumulative dose over 2 years, referred to as cladribine tablets 3.5 mg/kg) have shown efficacy across the spectrum of patients with relapsing multiple sclerosis (MS), including those at a higher risk of disease progression or with active disease while on a disease modifying drug (DMD) (Giovannoni et al., 2010; Giovannoni et al., 2011; Comi et al., 2013; Rammohan et al., 2012; Giovannoni et al., 2018; Giovannoni et al., 2017; Leist et al., 2014; Freedman et al., 2017; Montalban et al., 2016). Treatment with cladribine tablets leads to a transient reduction of lymphocyte counts and a minimal effect on innate immune function, followed by gradual reconstitution of the lymphocyte populations towards baseline levels (Giovannoni, 2017; Wiendl, 2017). By preferentially targeting lymphocytes, cladribine tablets can interfere with autoimmune processes underlying MS in which certain lymphocyte populations are considered to play a central role (Leist and Vermersch, 2007; Leist and Weissert, 2009).

The lymphocyte count reduction produced by cladribine tablets occurs earlier and to a greater extent in the case of $CD19^+$ B cells than in $CD4^+$ or $CD8^+$ T cells (Baker et al., 2017; Ceronie et al., 2018). However, the degree and time profile of the lymphocyte count reduction seen with cladribine tablets is distinct from that for alemtuzumab, where circulating lymphocytes are very significantly reduced after treatment (Baker et al., 2017; Dorr and Baum, 2016; Havrdova et al., 2017; Willis and Robertson, 2014; Thomas et al., 2016). The gradual recovery of lymphocyte populations following cladribine tablets occurs without the triggering of secondary autoimmunity observed following treatment with alemtuzumab (Zwang and Turka, 2014; Jones et al., 2009).

The mode of action of cladribine tablets is believed to be responsible for a durable clinical effect in patients with relapsing MS despite an only short-term presence of the therapeutic agent (Giovannoni et al., 2017). With long-term efficacy comes the need to consider long-term safety of cladribine tablets. Safety and tolerability outcomes from individual clinical studies with cladribine tablets have been reported previously (Giovannoni et al., 2010; Giovannoni et al., 2017; Leist et al., 2014; Cook et al., 2011). To provide a more comprehensive characterization of the safety profile of cladribine tablets in MS, data from these, and other relevant studies from the clinical development program have been combined for the purposes of an integrated analysis. This publication focuses on an integrated safety analysis of patients receiving oral monotherapy of cladribine tablets (Monotherapy Oral cohort) given as two courses of 4 or 5 days of treatment each year for 2 years to the cumulative dose of 3.5 mg/kg (the dose approved in Europe and other regions) (MAVENCLAD SmPC. 2017) or placebo. Data were derived from the three Phase III clinical trials (CLARITY [NCT00213135], CLARITY Extension [NCT00641537] and ORACLE-MS [NCT00725985]) as well as the ongoing Prospective observational long-term safety registry of multiple sclerosis patients who have participated in cladribine clinical trials (PREMIERE) registry (NCT01013350) in which patients continue to be followed up for long-term monitoring.

In addition, aggregated safety data on all cladribine exposed patients from studies and the on-going registry are also included (All Exposed cohort). This cohort includes data from all MS studies with cladribine (tablets or parenteral administration) or placebo, and data from ONWARD (NCT00436826) in which patients received cladribine tablets in combination with interferon (IFN)-β (Montalban et al., 2016). It also includes data from patients receiving other doses of cladribine tablets and for patients receiving treatment for more than 2 courses.

A companion publication in this journal issue (Comi et al., 2018) provides more detailed information on lymphocyte count changes. The protocols of clinical trials involving treatment with cladribine specified the use of contraception in study participants. Some pregnancies nevertheless occurred in some female study participants or female partners of male study participants. Available data from exposure during pregnancy will be reviewed in a separate publication.

2. Methods

2.1. Monotherapy Oral cohort

Safety data relating to treatment with cladribine tablets 3.5 mg/kg as oral monotherapy were combined from three Phase III studies (CLARITY, CLARITY Extension, and ORACLE-MS) that involved treatment with cladribine tablets 3.5 mg/kg and the PREMIERE registry (Supplementary Table 1) (Giovannoni et al., 2010; Giovannoni et al., 2017; Leist et al., 2014). This Monotherapy Oral cohort is the primary cohort as it evaluates the safety of oral cladribine given as monotherapy and includes long-term safety follow-up data.

CLARITY was a 96-week, Phase III, double-blind, randomized, placebo-controlled, parallel-group, multicenter study which evaluated the safety and efficacy of cladribine tablets 3.5 and 5.25 mg/kg (cumulative dose) in patients with relapsing-remitting MS (RRMS) (Giovannoni et al., 2010). CLARITY Extension was a 96-week, Phase IIIb, double-blind, randomized, parallel-group, multicenter, extension study which evaluated the safety, tolerability, and efficacy of treatment with cladribine tablets for an additional 2.5 years (including supplemental follow-up) beyond the 2-year CLARITY study. Eligibility for entry into CLARITY Extension was based upon completion of the double-blind treatment period in CLARITY. Patients who received cladribine tablets during the CLARITY study were randomized to receive an additional two courses of cladribine tablets or placebo. Patients who received placebo during CLARITY were assigned to two courses of cladribine tablets with a cumulative dose of 3.5 mg/kg (Giovannoni et al., 2017). ORACLE-MS was a 96-week Phase III, double-blind, randomized, placebo-controlled multicenter study which evaluated the safety and efficacy of 2 doses of treatment with cladribine tablets 3.5 and 5.25 mg/kg (cumulative dose) in patients with a first clinical demyelinating event, including patients who were subsequently found to have met the 2010 McDonald criteria (Leist et al., 2014; Freedman et al., 2017). The PREMIERE registry is a prospective, observational, long-term safety study of patients with MS that commenced in 2009 and is open to patients who had participated in one of the clinical studies of cladribine tablets (CLARITY, CLARITY Extension, ORACLE-MS or ONWARD). To enter PREMIERE, patients had to provide written informed consent.

2.2. All Exposed cohort

Safety relating to rarer adverse events of special interest (AESI), such as malignancies, was assessed in a larger All Exposed patient cohort. This cohort includes data from MS patients who received treatment with cladribine or placebo, regardless of the formulation or mode of administration and includes doses of cladribine higher than those recommended in the European Union (EU) Summary of Product Characteristics (SmPC) (MAVENCLAD SmPC. 2017). This All Exposed cohort analysis is most suitable for identifying and characterizing rare events but includes a more heterogeneous population than that

included in the trials studying cladribine tablets in relapsing MS patients. The All Exposed cohort additionally includes ONWARD which compared cladribine tablets or placebo in combination with IFN-β, and 5 other smaller trials in which patients were treated with placebo or parenteral cladribine (Supplementary Table 1).

2.3. Adverse events of special interest (AESI)

Three main categories of adverse events were defined as AESI; lymphopenia, infections and malignancies. Cladribine selectively reduces lymphocyte counts which may lead to lymphopenia (as expected from its mode of action). There is potential concern for an increase in the incidence of infections or malignancies associated with lymphopenia-associated immunosuppression and reduction of cell-mediated immunity. Malignancies, however, are generally observed only with profound and long-lasting immunosuppression (Comi et al., 2018; Oliveira Cobucci et al., 2012).

2.4. Analyses

All analyses were based on the safety analysis set for the relevant cohort (Monotherapy Oral or All Exposed), which comprised all patients receiving study treatment at least once (cut-off date of 20 February 2015). This corresponds to the data used as the basis of regulatory filings that supported the approval of cladribine tablets by the European Commission and other authorities, and the respective prescribing information (MAVENCLAD SmPC. 2017). Patients who received IFN-β per protocol as rescue therapy (CLARITY) or after conversion to clinically definite MS (ORACLE-MS) were included in the analyses.

All safety analyses were performed using the "as treated principle". For the Monotherapy Oral cohort, if patients received only placebo or were in the observational follow-up period without having switched subsequently to cladribine tablets, then their data became part of the placebo group. Patients who switched treatment from placebo to cladribine tablets in subsequent studies/periods (i.e. in CLARITY Extension), had their time on placebo censored at the time of the switch (Supplementary Table 2). Patients who switched treatment from placebo to cladribine tablets 3.5 mg/kg had their time on cladribine tablets 3.5 mg/kg initiated at the time of switching. Patients who were treated with cladribine tablets 3.5 mg/kg in CLARITY and were then re-exposed to cladribine tablets 3.5 mg/kg in a subsequent study/period (i.e. in CLARITY Extension) had their time on cladribine tablets 3.5 mg/kg censored at the time of re-exposure. Analysis of the All Exposed cohort used a conservative approach. Data from patients initially treated with cladribine and subsequently with placebo (i.e. in CLARITY Extension), were analyzed from the time of entry into the program as part of the cladribine group and never as part of the placebo group (Supplementary Table 2).

All integrated analyses were performed using SAS® Software version 9.2 or later. AEs and Medical Histories in all studies were recoded using the Medical Dictionary of Regulatory Activities (MedDRA) v17.1 in order to assure a common basis for the safety database. In addition, data from the Merck pharmacovigilance database were reconciled with the clinical database and the most current information was used in the analyses described. Data on AEs were based on treatment emergent adverse events (TEAEs), which were absent prior to treatment, but started during the treatment and observation period relative to the pre-treatment state. An AE was treatment-emergent if the AE occurred on or after day 1 during the treatment and observation period. Crude AE incidence rate was expressed as the sum of all patients with at least one occurrence of the AE of interest divided by the analysis population; Crude incidence rate = 100*(Number of patients with at least one AE/number of patients).

Assessments of AEs mainly used observation-adjusted incidence rates (Adj-AE), including Adj-AE per 100 patient-years (PY), the time-adjusted AE incidence rate which can be interpreted as the number of events occurring in 100-patient-years, calculated as 100*(Number of patients with at least one AE)/(Sum of observation time in days among patients at risk for initial occurrence of an AE or time on study/365.25). This presentation of AE incidence accounts for different observation periods between treatment groups and provides rates with reasonable decimal places based on the observation time and the number of events. Observation time until occurrence was calculated in a similar way to time on study but was limited to time to occurrence of the first AE of interest. For patients with no events, the time on study was used.

Analysis of malignancy events in the All Exposed cohort included all events in the clinical trial databases, irrespective of cladribine dose or route of administration. For the analysis of malignancies, data from the integrated clinical database (cut-off date 20 February 2015) were reconciled with the Merck pharmacovigilance database (cut-off date 05 November 2015). All cases with a reported preferred term within the Standardized MedDRA Query “Malignant or Unspecified Tumors” (MedDRA version 17.1) were identified, reviewed and assessed. In addition, all cases were adjudicated by an independent tumor review board on a case-by-case basis in a blinded fashion. Risk differences

Table 1
Demographic information for 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)
Time on study ≥ 24 weeks (~6 months), *n* (%)	617 (96.3)	900 (97.5)
Time on study ≥ 48 weeks (~1 year), *n* (%)	595 (92.8)	875 (94.8)
Time on study ≥ 96 weeks (~2 years), *n* (%)	486 (75.8)	772 (83.6)
Time on study ≥ 192 weeks (~4 years), *n* (%)	181 (28.2)	395 (42.8)
Time on study ≥ 384 weeks (~8 years), *n* (%)	60 (9.4)	93 (10.1)
Age (years), mean (SD)	36.6 (9.8)	36.5 (10.3)
Median	36.0	36.0
Min; max	18; 64	18; 65
Age ≤ 40 years, *n* (%)	415 (64.7)	592 (64.1)
Age > 40 years, *n* (%)	226 (35.3)	331 (35.9)
Male, *n* (%)	217 (33.9)	311 (33.7)
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)
Original study, *n* (%)		
CLARITY	435 (67.9)	685 (74.2)
ORACLE-MS	206 (32.1)	238 (25.8)

DMD, disease modifying drug; SD, standard deviation.
The Monotherapy Oral cohort includes data from CLARITY, CLARITY Extension, ORACLE-MS and PREMIERE.

(cladribine tablets vs. placebo) were presented with corresponding two-sided 95% confidence intervals (CIs) on Adj-AE per 100 PY, estimated by the Miettinen and Nurminen method (Miettinen and Nurminen, 1985) unless otherwise specified. Standardized Incidence Ratios (SIR) for adjudicated malignancies were calculated in relation to the GLOBOCAN 2012 reference population, (GLOBOCAN 2012) using the cut-off date of 20 February 2015.

3. Results

In both the Monotherapy Oral cohort and the All Exposed cohort the number of patients exposed to cladribine tablets at a cumulative dose of

Table 2
Summary of AEs for Monotherapy Oral cohort. See also Table 4 for infections and infestations.

	Placebo (*N* = 641)			Cladribine tablets 3.5 mg/kg (*N* = 923)		
	n	Total PY	Adj-AE per 100 PY	*n*	Total PY	Adj-AE per 100 PY
Patients with ≥ 1 TEAE	515	546.3	94.26	773	748.4	103.29
Patients with ≥ 1TEAE related to study drug	291	1162.8	25.03	542	1605.5	33.76
Patients with ≥ 1 serious‡ TEAE	67	1876.3	3.57	124	3096.8	4.00
Patients with TEAE leading to treatment discontinuation	21	1993.7	1.05	67	3229.0	2.07
Patients with ≥ 1 severe TEAE reported in ≥ 2 patients	57	1912.5	2.98	115	3111.2	3.70
Patients with TEAE leading to death†	5	2024.7	0.25	9	3431.0	0.26
***Most commonly reported TEAEs (Adj-AE per 100 PY of ≥1.0 in either group)**						
Nervous system disorders	**226**	**1429.5**	**15.81**	**327**	**2346.7**	**13.93**
Headache	144	1631.9	8.82	230	2641.9	8.71
Dizziness	36	1944.4	1.85	47	3268.0	1.44
Multiple sclerosis relapse [a]	11	2014.0	0.55	21	3404.9	0.62
Gastrointestinal disorders	**197**	**1454.9**	**13.54**	**278**	**2482.0**	**11.20**
Nausea	62	1845.6	3.36	86	3134.4	2.74
Diarrhea	44	1915.9	2.30	68	3202.0	2.12
Abdominal pain, upper	22	1969.2	1.12	42	3283.1	1.28
Toothache	22	1957.5	1.12	35	3335.8	1.05
Abdominal pain	23	1966.2	1.17	30	3346.2	0.90
Constipation	22	1968.7	1.12	24	3368.3	0.71
Vomiting	24	1982.6	1.21	21	3363.7	0.62
Blood and lymphatic system disorders	**47**	**1901.6**	**2.47**	**276**	**2543.4**	**10.85**
Lymphopenia	21	1985.0	1.06	217	2731.8	7.94
Leukopenia	8	2008.4	0.40	43	3276.9	1.31
Neutropenia	4	2015.0	0.20	27	3362.8	0.80
Musculoskeletal and connective tissue disorders	**153**	**1608.0**	**9.51**	**245**	**2654.5**	**9.23**
Back pain	46	1890.0	2.43	102	3115.8	3.27
Arthralgia	38	1938.8	1.96	63	3236.0	1.95
Pain in extremity	33	1965.6	1.68	50	3283.6	1.52
Myalgia	21	1966.3	1.07	28	3356.9	0.83
Musculoskeletal pain	16	1989.1	0.80	19	3375.9	0.56
General disorders and administration site conditions	**168**	**1558.5**	**10.78**	**213**	**2717.1**	**7.84**
Influenza-like illness	61	1857.4	3.28	75	3167.6	2.37
Fatigue	47	1897.2	2.48	54	3252.1	1.66
Pyrexia	20	1980.8	1.01	36	3341.5	1.08
Asthenia	25	1941.8	1.29	33	3311.5	1.00
Investigations	**83**	**1802.4**	**4.61**	**145**	**2939.6**	**4.93**
Lymphocyte count decreased	2	2023.1	0.10	26	3337.4	0.78
Psychiatric disorders	**85**	**1787.8**	**4.75**	**121**	**3009.3**	**4.02**
Insomnia	32	1938.7	1.65	46	3285.5	1.40
Depression	23	1960.6	1.17	46	3298.1	1.39
Anxiety	12	2002.3	0.60	37	3312.1	1.12
Respiratory, thoracic and mediastinal disorders	**95**	**1770.8**	**5.36**	**118**	**3065.2**	**3.85**
Oropharyngeal pain	35	1929.2	1.81	44	3278.8	1.34
Cough	27	1968.3	1.37	34	3336.6	1.02
Vascular disorders	**45**	**1909.6**	**2.36**	**72**	**3231.2**	**2.23**
Hypertension	25	1965.3	1.27	35	3338.5	1.05
Ear and labyrinth disorders	**35**	**1930.6**	**1.81**	**53**	**3269.0**	**1.62**
Vertigo	22	1966.4	1.12	35	3317.9	1.05
Injury, poisoning and procedural complications	**81**	**1830.4**	**4.43**	**115**	**3090.3**	**3.72**
Fall	13	1985.9	0.65	24	3371.1	0.71
Most commonly reported serious‡ TEAEs (Adj-AE per 100 PY of ≥ 0.10 in either group)						
Blood creatine phosphokinase increased	4	2022.6	0.20	7	3414.4	0.21
Pneumonia	3	2019.7	0.15	6	3403.4	0.18
Uterine leiomyoma	2	2020.9	0.10	5	3409.7	0.15
Lymphopenia	0	2026.0	0	4	3421.4	0.12
Urinary tract infection	1	2024.4	0.05	4	3419.4	0.12

n is the number of patients with events; T is the total patient's time on study in years. If a patient has multiple events, the time to first event is considered. For a patient with no event the time is censored at the last follow-up time for that patient.
Adj-AE per 100 PY is the time adjusted AE incidence rate which can be interpreted as the number of events occurring in 100 patient-years.
*System organ class and preferred terms are presented in descending order of Adj-AE per 100 PY rate in the cladribine tablets 3.5 mg/kg group.
‡Serious was defined as resultant in death; life-threatening; required inpatient hospitalization; congenital anomaly or birth defect; or was otherwise considered as medically important.
†Narratives for deaths in the Monotherapy Oral and All Exposed cohorts are shown in Supplementary Table 4
[a] Preferred term "Multiple sclerosis relapse" was reported in PREMIERE where relapse was not an efficacy endpoint.

3.5 mg/kg was larger and had a longer average time period of follow up compared to the number who received placebo (Table 1). The larger numbers of patients exposed to cladribine tablets reflects the fact that in both cohorts patients may have switched from placebo to cladribine tablets in CLARITY Extension; additionally, in the All Exposed cohort several large studies included a higher number of patients exposed to cladribine (at all doses) than placebo. In the Monotherapy Oral cohort, the median age of patients who received placebo and those who were treated with cladribine tablets 3.5 mg/kg was similar, at about 36 years at the time of enrollment into the respective trial. The majority of patients in each group were women. Disease characteristics were balanced in both groups. A similar pattern of patient characteristics was seen in the demographics of the All Exposed cohort (Supplementary Table 3).

3.1. Summary of adverse events

The incidence rate of TEAEs in the Monotherapy Oral cohort was 103.29 vs. 94.26 Adj-AEs per 100 PY for placebo (Table 2). There was a trend for a higher rate of drug-related TEAEs with cladribine tablets 3.5 mg/kg vs. placebo (33.76 vs. 25.03 Adj-AEs per 100 PY, respectively). The rate of TEAEs leading to treatment discontinuation was low across both the cladribine tablets 3.5 mg/kg and placebo groups (2.07 and 1.05 Adj-AE per 100 PY, respectively). The number of patients with TEAEs leading to death was very low, and was similar in the cladribine tablets 3.5 mg/kg and placebo groups (0.26 and 0.25 Adj-AE per 100 PY, respectively). Listings and brief narratives for deaths in the Monotherapy Oral and All Exposed cohorts including those occurring during the registry phase are shown in Supplementary Table 4.

Headache was the most common TEAE (8.71 per 100 PY for cladribine tablets 3.5 mg/kg and 8.82 per 100 PY for placebo). Hematologic TEAEs occurring at a higher rate with cladribine tablets (≥0.5 Adj-AE per 100 PY) were, in decreasing order of frequency, lymphopenia, leukopenia and neutropenia (Table 2). TEAEs that were less frequent with cladribine tablets than placebo (≥0.5 Adj-AE per 100 PY) included urinary tract infection (2.40 for placebo vs. 1.69 for cladribine tablets 3.5 mg/kg), and influenza-like illness (3.28 for placebo vs. 2.37 for cladribine tablets 3.5 mg/kg) which may be related to IFN-β rescue therapy being required more frequently in patients randomized to placebo.

Serious AEs (SAEs) were reported with an Adj-AE per 100 PY rate of 4.00 in the cladribine tablets 3.5 mg/kg group vs. 3.57 for placebo. Except for lymphopenia (Adj-AE per 100 PY 0.12 vs. 0 for placebo; Table 2) the rate of SAEs with cladribine tablets was comparable to that for placebo. Details of the most frequently reported SAEs with an adjusted rate of ≥0.05 per 100 PY are shown in Supplementary Table 5.

3.2. Effects of cladribine tablets on lymphocyte counts

Lymphocyte count reductions are expected due to the mechanism of action of cladribine. The effects of cladribine tablets on lymphocyte counts in the Monotherapy Oral cohort are shown in Table 3. In the CLARITY and CLARITY Extension studies, Grade 3 lymphopenia (absolute lymphocyte count [ALC] 0.2– $< 0.5 \times 10^9$ cells/L) was experienced by 25% of patients and Grade 4 lymphopenia ($< 0.2 \times 10^9$ cells/L) was experienced by < 1% of patients treated with cladribine tablets 3.5 mg/kg (Giovannoni et al., 2010; Giovannoni et al., 2017). It is of note that the Monotherapy Oral cohort included patients with IFN-β as rescue medication (patients who received IFN-β as rescue medication were not excluded or censored). The companion publication (Comi et al., 2018) provides more detailed information on lymphocyte changes in relation to treatment using a cohort of patients that does not include those from ORACLE-MS (Leist et al., 2014). That analysis demonstrates that after rapid reductions in the lymphocyte count, lymphocyte count recovery begins soon after treatment with cladribine tablets 3.5 mg/kg in year 1 and year 2. In patients that met the treatment guidelines specified in the EU SmPC for cladribine tablets (MAVENCLAD SmPC. 2017), severe (Grade 3/4; $< 0.5 \times 10^9$ cells/L) lymphopenia was uncommon (MAVENCLAD SmPC. 2017; Cook et al., 2017).

3.3. Summary of infections

The incidence rate for infections overall, severe infections, infections leading to discontinuation, or opportunistic infections, was comparable following cladribine tablets 3.5 mg/kg and placebo (Table 4). The incidence of herpes zoster and herpetic infections was increased following cladribine tablets 3.5 mg/kg versus placebo. For the AESI herpetic infections, herpes zoster was the most frequently reported preferred term for patients randomized to cladribine tablets 3.5 mg/kg, followed by oral herpes and herpes simplex (see Table 4). A time to event analysis indicated that more events occurred shortly after treatment with cladribine tablets 3.5 mg/kg in years 1 and 2, but the low number of overall events does not allow conclusions to be drawn (Supplementary Fig. 1).

Herpes zoster cases were all dermatomal and followed a normal course. There were no cases of post herpetic neuralgia reported in patients treated with cladribine tablets. The Adj-AE per 100 PY for serious

Table 3
Effects of cladribine tablets on lymphocyte counts for the Monotherapy Oral cohort.

Time point	Placebo (*N* = 641)	Cladribine tablets 3.5 mg/kg (*N* = 923)
Baseline		
N (missing)	640 (1)	921 (2)
Median (IQR) cell count, 10^9/L	1.918 (1.560; 2.330)	1.870 (1.520; 2.300)
Week 9 (nadir year 1)		
N (missing)	607 (25)	873 (43)
Median (IQR) cell count, 10^9/L	1.890 (1.560; 2.280)	1.030 (0.790; 1.300)
Median (IQR) cell count reduction from baseline, 10^9/L	−0.005 (− 0.300; 0.260)	−0.830 (− 1.155; −0.515)
Week 48		
N (missing)	395 (205)	587 (290)
Median (IQR) cell count, 10^9/L	1.880 (1.530; 2.270)	1.220 (0.960; 1.500)
Median (IQR) cell count reduction from baseline, 10^9/L	−0.030 (−0.320; 0.280)	−0.660 (−940; −0.400)
Week 55 (nadir year 2)		
N (missing)	280 (306)	538 (330)
Median (IQR) cell count, 10^9/L	1.900 (1.565; 2.345)	0.815 (0.600; 1.070)
Median (IQR) cell count reduction from baseline, 10^9/L	0.010 (− 0.360; 0.300)	−1.075 (− 1.440; − 0.730)
Week 96		
N (missing)	438 (104)	668 (155)
Median (IQR) cell count, 10^9/L	1.900 (1.525; 2.280)	1.043 (0.810; 1.340)
Median (IQR) cell count reduction from baseline, 10^9/L	−0.065 (− 0.320; 0.290)	− 0.800 (−1.110; − 0.500)

Table 4
Summary of infections and infestations for the Monotherapy Oral cohort.

	Placebo (*N* = 641)			Cladribine tablets 3.5 mg/kg (*N* = 923)		
	n	Total PY	Adj-AE per 100 PY	n	Total PY	Adj-AE per 100 PY
***Most commonly reported TEAEs in SOC Infections and Infestations (Adj-AE per 100 PY of ≥ 1.0 in either group)**	**314**	**1160.8**	**27.05**	**478**	**1917.5**	**24.93**
Nasopharyngitis	97	1764.5	5.50	158	2951.0	5.35
Upper respiratory tract infection	61	1869.1	3.26	109	3112.0	3.50
Influenza	51	1898.1	2.69	87	3169.5	2.74
Bronchitis	22	1964.4	1.12	55	3234.1	1.70
Urinary tract infection	46	1916.8	2.40	55	3249.7	1.69
Herpes zoster	4	2019.0	0.20	28	3360.2	0.83
Pharyngitis	31	1961.4	1.58	27	3348.0	0.81
Rhinitis	22	1962.3	1.12	24	3354.0	0.72
Serious‡ TEAEs in SOC Infections and infestations (Adj-AE of ≥ 0.05 in either group)	**10**	**2003.4**	**0.50**	**23**	**3357.6**	**0.69**
Appendicitis	2	2023.5	0.10	1	3426.8	0.03
Chronic Hepatitis C	1	2019.4	0.05	0	3432.7	0
Chronic sinusitis	1	2024.1	0.05	0	3432.7	0
Erysipelas	1	2022.1	0.05	0	3432.7	0
Herpes zoster	0	2026.0	0	2	3425.6	0.06
Myocarditis bacterial	1	2024.2	0.05	0	3432.7	0
Pneumonia	3	2019.7	0.15	6	3403.4	0.18
Pyelonephritis	0	2026.0	0	2	3423.1	0.06
Urethral abscess	1	2025.9	0.05	1	3430.3	0.03
Urinary tract infection	1	2024.4	0.05	4	3419.4	0.12
Infections and infestations SOC leading to treatment discontinuation (Adj-AE of ≥ 0.01 in either group)	3	2020.8	0.15	4	3415.5	0.12
Hepatitis B	0	2026.0	0	1	3427.9	0.03
Herpes zoster	0	2026.0	0	1	3424.8	0.03
Pneumonia bacterial	0	2026.0	0	1	3428.2	0.03
Urinary tract infection	0	2026.0	0	1	3432.6	0.03
Appendicitis	1	2025.8	0.05	0	3432.7	0
Gardnerella infection	1	2025.8	0.05	0	3432.7	0
Varicella	1	2021.0	0.05	0	3432.7	0
AESI severe infection (Adj-AE of ≥ 0.05 in any group)	**17**	**1983.4**	**0.86**	**28**	**3336.2**	**0.84**
Pneumonia	3	2109.7	0.15	6	3403.4	0.18
Urinary tract infection	2	2023.4	0.10	4	3419.4	0.12
Herpes zoster	1	2024.4	0.05	3	3424.1	0.09
Gastroenteritis	0	2026.0	0	2	3423.8	0.06
Pyelonephritis	0	2026.0	0	2	3423.1	0.06
AESI Opportunistic infections	23	1965.5	1.17	36	3321.9	1.08
Axillary candidiasis	1	2018.3	0.05	0	3432.7	0
Fungal infection	2	2023.4	0.10	8	3398.3	0.24
Fungal skin infection	2	2018.4	0.10	3	3430.8	0.09
Mastitis fungal	1	2025.6	0.05	0	3432.7	0
Onychomycosis	3	2023.1	0.15	4	3419.0	0.12
Oral candidiasis	1	2021.6	0.05	1	3431.0	0.03
Oral fungal infection	2	2013.9	0.10	1	3431.5	0.03
Pulmonary tuberculosis	0	2026.0	0	1	3429.6	0.03
Skin candida	1	2025.4	0.05	0	3432.7	0
Tonsillitis fungal	1	2022.0	0.05	0	3432.7	0
Tuberculosis	0	2026.0	0	1	3432.7	0.03
Upper respiratory fungal infection	0	2026.0	0	1	3431.7	0.03
Urinary tract infection fungal	0	2026.0	0	1	3424.1	0.03
Vulvovaginal candidiasis	3	2013.3	0.15	7	3416.9	0.20
Vulvovaginal mycotic infection	7	2016.4	0.35	9	3402.0	0.26
AESI Herpetic infections	19	1969.9	0.96	60	3262.7	1.84
Herpes zoster	4	2019.0	0.20	28	3360.2	0.83
Oral herpes	11	1996.9	0.55	20	3381.3	0.59
Herpes simplex	1	2018.1	0.05	5	3416.6	0.15
Herpes virus infection	1	2020.6	0.05	4	3416.9	0.12
Varicella	2	2020.6	0.10	3	3422.6	0.09
Herpes zoster disseminated	1	2023.7	0.05	2	3427.5	0.06
Genital herpes	0	2026.0	0	1	3429.0	0.03
AESI Herpes zoster**	4	2017.7	0.20	29	3356.2	0.86
Herpes zoster	4	2019.0	0.20	28	3360.2	0.83
Herpes zoster disseminated	1	2023.7	0.05	2	3427.5	0.06

*System organ class and preferred terms are presented in descending order of Adj-AE per 100 PY rate in the cladribine tablets 3.5 mg/kg group.
‡Serious was defined as resultant in death; life-threatening; required inpatient hospitalization; congenital anomaly or birth defect; or was otherwise considered as medically important.
n is the number of patients with events; Total PY is the total patient's time on study in years. If a patient has multiple events, the time to first event is considered. For a patient with no event the time is censored at the last follow-up time for that patient.
AESI = Severe infection is a custom grouping defined by any serious or severe event belonging to the MedDRA SOC Infections and infestations.
AESI = Medical Concept Opportunistic Infection is a custom query containing all PTs belonging to the medical concept of opportunistic infections excluding the PTs belonging to the HLT Herpes viral infections.
** From AESI = Medical concept herpetic infection, which is a custom grouping defined by PTs with the term 'herpes zoster'.

Table 5
Incidence rates, risk difference and risk ratio for malignancies in patients treated with cladribine or placebo.

Monotherapy Oral cohort	Placebo (N = 641)	Cladribine tablets 3.5 mg/kg (N = 923)
n/ PY at risk	3/2022.11	10/3414.20
Incidence per 100 PY	0.14836	0.29289
95% CI of incidence[a]	0.0478–0.4600	0.1576–0.5444
Risk Difference per 100 PY		0.1445
95% CI of Risk Difference per 100 PY[b]		−0.1656–0.4141
Risk Ratio		1.9742
95% CI of Risk Ratio[c]		0.5433–7.1733
All Exposed cohort	Placebo (N = 802)	Cladribine (N = 1976)
n/ PY at risk	4/2357.09	32/8579.39
Incidence per 100 PY	0.16970	0.37299
95% CI of incidence[a]	0.0637–0.4522	0.2638–0.5274
Risk Difference per 100 PY		0.2033
95% CI of Risk Difference per 100 PY[b]		−0.0785–0.3947
Risk ratio		2.1979
95% CI of Risk Ratio[c]		0.7773–6.2148

CI, confidence interval; n, number of patients with events; PY, patient year.
[a] CI computed with the exact Clopper–Pearson formula.
[b] CI computed using the Miettinen and Nurminen method.
[c] CI computed with the Wald method for the number of subject with events using a Poisson regression model with fixed effect for treatment group and log of time at risk as an offset.

or severe herpes zoster was 0.09 with cladribine tablets 3.5 mg/kg and 0.05 with placebo. The incidence rate of serious or severe infections was low in the cladribine tablets 3.5 mg/kg group and no relevant differences vs. placebo were observed at the preferred term level (Table 4; AESI Severe infection is a custom grouping defined by any serious or severe event belonging to the MedDRA SOC Infections and infestations).

The incidence of opportunistic infections was similar for cladribine tablets 3.5 mg/kg (1.08 Adj-AE per 100 PY) and placebo (1.17 Adj-AE per 100 PY). More than half of the opportunistic infections were mucocutaneous and cutaneous fungal infections, which resolved on standard treatments. Opportunistic infections that could be life-threatening (e.g., progressive multifocal leukoencephalopathy, cryptococcosis, toxoplasmosis, pneumocystis jirovecii pneumonia, cytomegalovirus infection or listeriosis) were not observed in the cladribine trials or during the subsequent registry period.

3.4. Infections during periods of grade 3 or 4 lymphopenia

A post-hoc analysis specifically examined the infectious AEs and SAEs occurring during periods of Grade 3 or 4 lymphopenia in patients treated with cladribine tablets 3.5 mg/kg. Periods of Grade 3 or 4 lymphopenia were defined as the onset of the Grade 3 or 4 lymphopenia (ALC $< 0.5 \times 10^9$ cells/L) until recovery to ALC $> 0.5 \times 10^9$ cells/L, plus 2 weeks.

During periods of Grade 3 and 4 lymphopenia infections occurred with increased frequency. The type of infectious events reported during Grade 3 and 4 lymphopenia did not differ from those occurring outside of these periods (Supplementary Table 6). Herpes zoster occurred more frequently during these periods (Adj AE per 100 PY 4.50 vs. 0.73 without Grade 3 or 4 lymphopenia). The clinical profile of herpes zoster was uncomplicated, consistent with findings for the overall Monotherapy Oral cohort.

Upper respiratory tract infections were reported more frequently during periods of Grade 3 or 4 lymphopenia. Overall, there was a low incidence of opportunistic infections during severe lymphopenia; the incidence was similar for patients in the cladribine tablets 3.5 mg/kg and placebo groups. The only opportunistic infections reported during Grade 3 or 4 lymphopenia were single occurrences in the preferred terms 'Urinary tract infection fungal' and 'Fungal infection' . None of

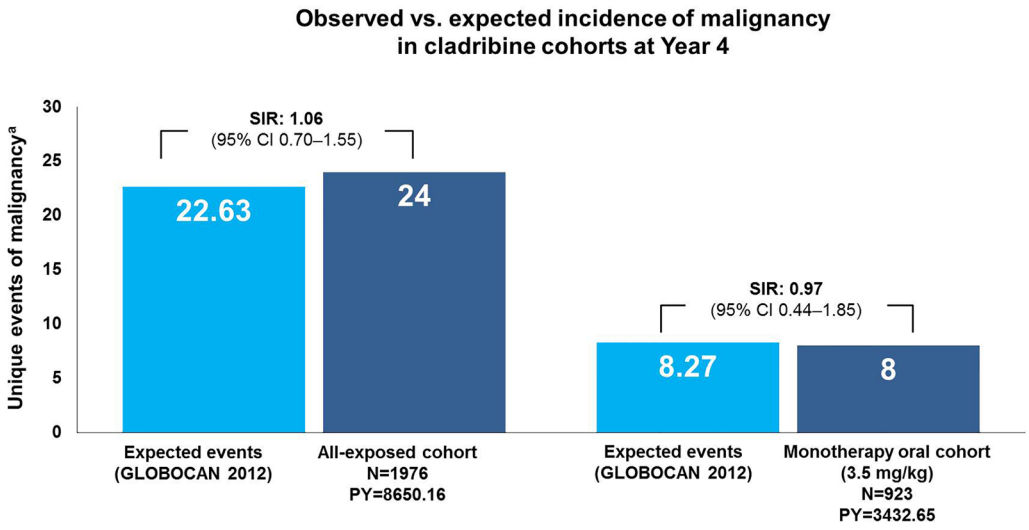

Fig. 1. Malignancy incidence for cladribine compared with external reference populations. [a]SIR calculated against the GLOBOCAN reference population (non-melanoma skin cancer excluded due to inconsistent reporting in GLOBOCAN). Reference population (GLOBOCAN 2012), http://globocan.iarc.fr/default.aspx. PY, patient-years; SIR, standardized incidence ratio.

these events were severe or serious.

4. Malignancy risk

Cladribine is a prodrug which is phosphorylated intracellularly to its active form, 2-chlorodeoxyadenosine triphosphate (Cd-ATP), by deoxycytidine kinase, and Cd-ATP is degraded by 5′-nucleotidase. B and T lymphocytes contain a higher deoxycytidine kinase to 5′-nucleotidase activity ratio than other cells types, which means Cd-ATP accumulates selectively to high levels in these cells, leading to their apoptosis (Leist and Vermersch, 2007; Carson et al., 1986; S. Seto et al., 1986; S. Seto et al., 1986; Saven and Piro, 1994). Cladribine's clinical efficacy is thought to be due to selective reduction and subsequent repopulation of both B and T cells. In view of cladribine's mechanism of action the risk of malignancy was thoroughly evaluated in the clinical program. In the integrated analysis of the clinical trials and the registry follow-up of cladribine in MS, no significant increase of malignancies has been observed. In particular there was no increase in the types of malignancies known to be associated with severe immunosuppression (e.g. non melanoma skin cancer, virally associated tumors and hematological malignancies).

While there was an imbalance in the total number of cases of malignancies observed in the cladribine tablets 3.5 mg/kg group compared to placebo, this was not meaningful after adjustment for number of patients, risk and different follow-up times. For estimation of any incremental effect of cladribine tablets 3.5 mg/kg over placebo, the risk of malignancy was assessed by examining the risk difference. Risk difference (RD) per 100 PY and risk ratios (RR) are shown in Table 5. The 95% confidence intervals of RD and RR include 0 and 1, respectively, supporting the conclusion that the current evidence does not indicate an increased risk of malignancies with cladribine treatment.

Hematologic or lymphoproliferative cancers were not observed following exposure to cladribine in either the Monotherapy Oral or All Exposed cohorts as might have been expected from an agent activated in lymphocytes, and there was no clustering of specific tumor types as might have been expected if cladribine were carcinogenic (See Supplementary Table 7).

4.1. Comparison with external reference populations

For the Monotherapy Oral cohort, the analysis of the malignancy SIR showed that the rate of malignancies observed with cladribine tablets 3.5 mg/kg was almost identical (0.97, 95% CI 0.44–1.85) to the expected rate of malignancies from the GLOBOCAN matched reference population (Fig. 1). Analysis of the malignancy SIR for the All Exposed cohort showed that the rate of malignancies compared to the GLOBOCAN matched reference population was similar following cladribine exposure (1.06, 95% CI 0.70–1.55) (Fig. 1). The GLOBOCAN database does not include data on non-melanoma skin cancers (NMSCs), therefore, an epidemiologic database from Denmark, a country with low NMSC incidence rates, was used for external comparison (Birch-Johansen et al., 2010). This showed no increase in incidence of NMSC

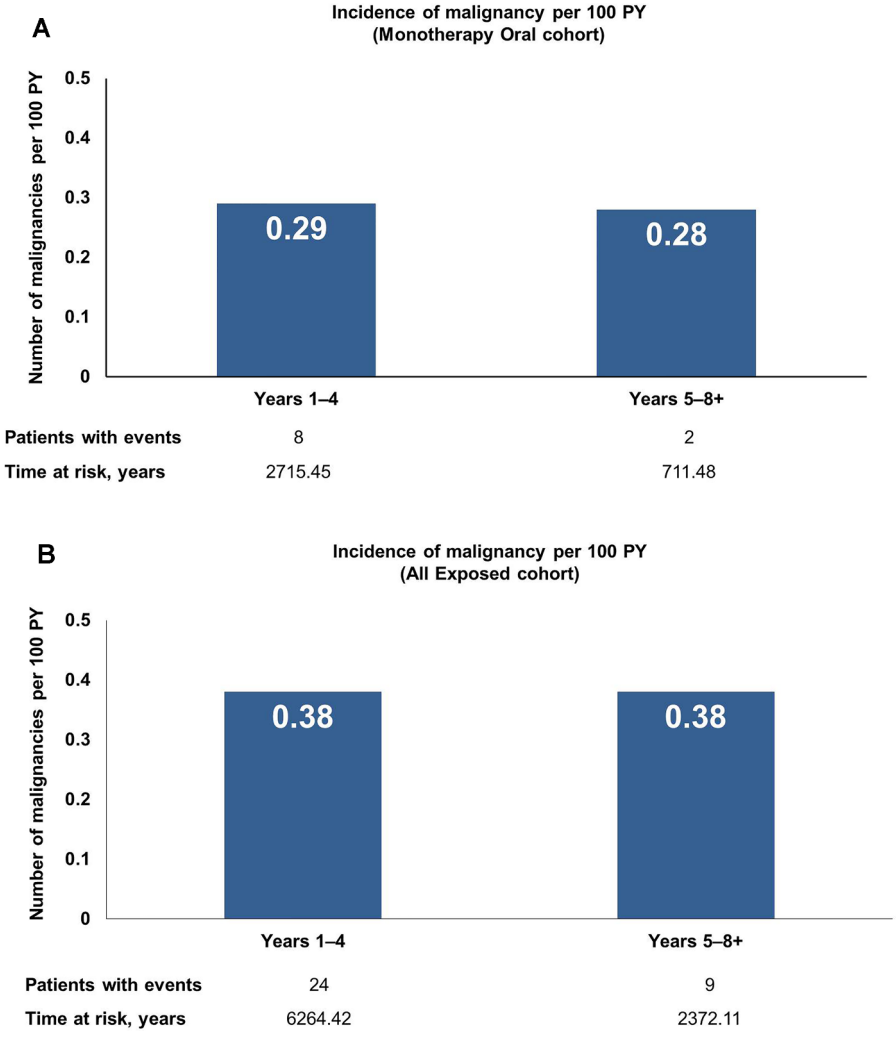

Fig. 2. Risk of malignancy over time for cladribine in the Monotherapy Oral cohort (A) or All Exposed cohort (B).

for cladribine compared to the reference database (data not shown).

4.2. Risk of malignancies over time

There was no increase in the risk of malignancy over time (Fig. 2). In the Monotherapy Oral cohort, the malignancy rate for cladribine tablets 3.5 kg/mg during years 1–4 (0.29 Adj-AE per 100 PY) was very close to the rate during years 5–8+ (0.28 Adj-AE per 100 PY), indicating that the malignancy incidence rate was constant during these 2 periods. In contrast, the malignancy rate in the placebo group was higher during years 5–8+ (0.60 Adj-AE per 100 PY) than during years 1–4 (0.06 Adj-AE per 100 PY), but the overall number of events was small. In the All Exposed cohort, the malignancy rate for cladribine during years 1–4 (0.38 Adj-AE per 100 PY) was identical to the rate during years 5–8 + , demonstrating that the malignancy rate remained constant over time (Fig. 2). In the placebo group, the malignancy rate in years 1–4 was 0.10 and during years 5–8+ it was 0.57.

4.3. Comparison of overall experience for cladribine and other disease modifying drugs

The overall malignancy incidence rate of cladribine (both Monotherapy Oral and the All Exposed cohort) was compared with data for other DMDs (using mainly regulatory sources except in the case of fingolimod) (Table 6). This showed that the incidence rate for the Monotherapy Oral and All Exposed cohorts is similar to the rates reported for other DMDs.

5. Discussion

The integrated analyses reported here show that the AE profile and safety for cladribine tablets 3.5 mg/kg as monotherapy are favorable overall. This safety profile should be considered in the context of the clinical efficacy and its durable effect. Given the unique treatment schedule of cladribine tablets, an important consideration is subsequent therapy. A post-hoc analysis of patients with relapsing MS treated with cladribine tablets 3.5 mg/kg as monotherapy (in CLARITY, CLARITY Extension or ORACLE-MS and followed up in PREMIERE) suggested that only a minority received a subsequent DMD (for any reason) after treatment with cladribine tablets. At 4 years after last dose of cladribine tablets, the Kaplan-Meier estimated proportion of patients who had initiated another DMD was 26.8% (95% CI: 22.2–31.5%); see Supplementary Information for details.

Cladribine tablets are given over 2 weeks (each with 4 or 5 treatment days) per year for 2 years (cumulative dose 3.5 mg/kg), followed by no treatment with cladribine for the next 2 years. For a treatment such as cladribine tablets with its durable efficacy, the relevant observation period for safety extends well beyond the time when study treatment is being administered. Therefore, observation periods are not directly linked to periods of active treatment or placebo and incidence rates may change during longer observation periods. The safety data analyzed here is presented as observation-adjusted incidence rates per 100 patient years of exposure and follow-up time. This is done to account for different follow-up times in the treatment arms. In this context, estimates for some events which have occurred in the short term after drug exposure may be diluted by accounting for longer exposure times. However, previous publications of individual studies (e.g. CLARITY) have described adverse events in comparison to placebo in the short term (2 year) context (Giovannoni et al., 2010; Giovannoni et al., 2017; Leist et al., 2014) and the results from these short-term analyses were broadly similar to those from the analyses presented here. The long-term analyses in this report are particularly useful in analyzing the incidence of rare events and events that take time to be observed, and comparison with other safety databases was useful in providing context for these data.

Lymphopenia is an expected effect of treatment with cladribine tablets due to the mechanism of action. In a companion paper, providing details of lymphocyte changes over time, it is shown that after the initial reduction in lymphocyte count numbers, their recovery begins soon after treatment with cladribine tablets in year 1 and year 2 (Comi et al., 2018). The majority of patients treated with cladribine tablets 3.5 mg/kg in clinical trials (around 75%) did not experience Grade 3/4 lymphopenia (ALC $< 0.5 \times 10^9$ cells/L) over the 2 years of treatment and Grade 4 (ALC $< 0.2 \times 10^9$ cells/L) at any time over the 2 years was experienced by < 1% of patients (MAVENCLAD SmPC. 2017). In general, there was no increase in the risk of infections including opportunistic infections with cladribine tablets versus placebo, except for herpes zoster. There were no cases of systemic, serious or disseminated herpes zoster attributed to treatment with cladribine tablets. Occurrences of severe lymphopenia (ALC $< 0.5 \times 10^9$ cells/L) resulted in an increased frequency of infections, but the nature of these was not different to that observed in the overall patient group treated with cladribine tablets 3.5 mg/kg. In general, patients with Grade 4 lymphopenia are more susceptible to infections, but these actually occurred infrequently in patients treated with cladribine tablets 3.5 mg/kg. The EU SmPC for cladribine tablets states that if lymphocyte counts drop to $< 0.2 \times 10^9$ cells/L during treatment, anti-herpes prophylaxis according to local standard practice should be considered during the time of Grade 4 lymphopenia (MAVENCLAD SmPC. 2017).

Analysis of malignancy rates in the overall clinical program of cladribine in MS does not indicate an increase compared to placebo-treated patients, either in the All Exposed cohort or the Monotherapy Oral cohort. With regards to epidemiologic 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 malignancies observed in the cladribine program were typical of those seen in the general population with no increase in the incidence of malignancies over time in cladribine-treated patients. There was no clustering of malignancies of any particular type, and no increase in malignancies commonly associated with immunosuppression were observed (hematologic, virally induced or non-melanoma skin cancers). Given the limitations of the clinical trial population on identifying rare

Table 6
Comparison of overall malignancy incidence rate of cladribine (both Monotherapy Oral and the All Exposed cohort) and other disease modifying drugs in multiple sclerosis patient populations.

Disease modifying drug	Incidence rate (cases per 100 PY)
Cladribine tablets 3.5 mg/kg – Monotherapy Oral cohort	0.29
Cladribine – All Exposed cohort	0.37
Alemtuzumab (Lemtrada CDER Background Package 2013)	0.37
Natalizumab (Tysabri FDA Medical Review 2004)	0.32
Fingolimod (Kappos et al., 2014)	1.19
Dimethyl fumarate (Tecfidera RMP v5. Biogen Idec 2013)	0.38
Ocrelizumab (Ocrevus CDER Medical Review 2016)	0.40

PY, patient-year

adverse events and in order to further monitor and characterize the long-term safety profile of cladribine tablets, an 8000-patient post-authorization safety study comparing cladribine tablets with fingolimod is being conducted.

6. Conclusions

The AE profile for cladribine tablets 3.5 mg/kg as a monotherapy has been well-characterized in a pooled population of patients from early to more advanced relapsing MS. Lymphopenia is expected from the mode of action of cladribine tablets, and treatment guidelines reduce the incidence of severe and prolonged lymphopenia with cladribine treatment, while preserving durable efficacy. In general, there was no increased risk for infections with cladribine tablets 3.5 mg/kg Monotherapy, except for a higher incidence of herpes zoster. Severe lymphopenia (ALC $< 0.5 \times 10^9$ cells/L) resulted in an increased frequency of infections. However, the infectious AE profile observed during periods of Grade 3 and 4 lymphopenia did not differ from that seen outside of these periods. Analysis of the totality of the safety data in the clinical program in MS does not indicate an increased risk of malignancies with cladribine.

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Conflict of interest statements

SC has received honoraria for lectures/consultations from Merck, Bayer HealthCare, Sanofi-Aventis, Neurology Reviews, Biogen Idec, Teva Pharmaceuticals, and Actinobac Biomed Inc.; has served on advisory boards for Bayer HealthCare, Merck, Actinobac Biomed, Teva Pharmaceuticals, and Biogen Idec; and received grant support from Bayer HealthCare.

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XM has been a steering committee member of clinical trials or participated in advisory boards of clinical trials with Actelion, Bayer, Biogen, Celgene, Genzyme, Merck, Novartis, Oryzon, Roche, Sanofi-Genzyme and Teva Pharmaceutical.

GG has received speaker honoraria and consulting fees from Abbvie, Actelion, Atara Bio, Almirall, Bayer Schering Pharma, Biogen Idec, FivePrime, GlaxoSmithKline, GW Pharma, Merck, Pfizer Inc, Protein Discovery Laboratories, Teva Pharmaceutical Industries Ltd, Sanofi-Genzyme, UCB, Vertex Pharmaceuticals, Ironwood, and Novartis; and has received research support unrelated to this study from Biogen Idec, Merck, Novartis, and Ironwood.

AN, CH and ES are employees of Merck KGaA, Darmstadt, Germany

AG is an employee of Merck, Aubonne, Switzerland, a division of Merck KGaA, Darmstadt, Germany.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2018.11.021.

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