Multiple Sclerosis and Related Disorders 46 (2020) 102572

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Original article

Long-term safety data from the cladribine tablets clinical development program in multiple sclerosis

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ARTICLE INFO

Keywords:
Cladribine tablets
Multiple sclerosis;, Safety
Long-term

ABSTRACT

Background: Long-term safety data are of particular interest for any newly approved treatment in multiple sclerosis such as cladribine tablets 10 mg (MAVENCLAD®; 3.5 mg/kg cumulative dose over 2 years, referred to as cladribine tablets 3.5 mg/kg), which is approved in Europe and the USA. Here we provide the final report on the integrated analysis of the safety profile of cladribine tablets 3.5 mg/kg from the clinical development program, including final data from the PREMIERE registry.

Methods: Safety data for cladribine tablets 3.5 mg/kg from three previously reported Phase III studies (CLARITY, CLARITY Extension and ORACLE-MS), as well as the prospective, observational PREMIERE registry (which ran from November 2009 to October 2018; consisting of patients who had participated in at least one of the Phase III trials) were combined to provide the Monotherapy Oral cohort. Serious adverse events (SAEs) and predefined SAEs of special interest were recorded. Observation-adjusted incidence rates per 100 patient-years (Adj-AE per 100 PY) were used to assess adverse events (AEs). Standardized incidence ratios for malignancies were calculated in relation to a matched GLOBOCAN reference population, and risk differences (cladribine tablets versus placebo) were estimated.

Results: The Monotherapy Oral cohort comprised 923 patients who received cladribine tablets 3.5 mg/kg and 641 patients who received placebo. Overall, the reported number of SAEs was higher in the cladribine tablets 3.5 mg/kg group (133/923 [14.4%] patients with at least 1 SAE), versus the placebo group (68/641 [10.6%] patients with at least 1 SAE). Four patients in the cladribine tablets 3.5 mg/kg group had lymphopenia classified as a serious event (resulting in an Adj-AE of 0.10 per 100 PY) and 2 patients had serious herpes zoster (resulting in an Adj-AE of 0.05 per 100 PY). There were no cases in the corresponding placebo groups. There was no difference between the cladribine tablets 3.5 mg/kg group and placebo in the overall incidence of infections. However herpetic infection AEs occurred more frequently in the cladribine tablets 3.5 mg/kg group (driven primarily by herpes zoster, followed by oral herpes and herpes simplex). Overall, there was a numerical imbalance in malignancy incidence between cladribine tablets 3.5 mg/kg and placebo, with an Adj-AE of 0.26 and 0.12 per 100 PY, respectively; however the difference was not statistically significant. The rate of malignancies observed with cladribine tablets 3.5 mg/kg in the final integrated safety analysis was not different from the expected rate in the matched GLOBOCAN reference population (standardized incidence ratio, 0.88; 95% CI, 0.44–1.69).

Conclusion: Additional patient-years of observation do not significantly alter the conclusions of earlier interim analyses, and no new major safety findings were identified in this consolidated analysis of safety data of cladribine tablets 3.5 mg/kg monotherapy in patients with relapsing-remitting multiple sclerosis.

Abbreviations: Adj-AE per 100 PY, observation-adjusted incidence rates per 100 patient-years; AE, adverse event; AESI, AEs of special interest; NMSC, non-melanoma skin cancer; RRMS, relapsing-remitting MS; SAE, serious adverse event; SIR, standardized incidence ratio; TEAE, treatment-emergent adverse event

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https://doi.org/10.1016/j.msard.2020.102572
Received 3 July 2020; Received in revised form 6 October 2020; Accepted 7 October 2020
Available online 08 October 2020

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 been approved in Europe and many other countries, including the USA. Cladribine tablets 3.5 mg/kg are administered for 2 weeks over 2 months as two annual courses and show durable efficacy in patients with relapsing multiple sclerosis (MS) (Giovannoni et al., 2010; Giovannoni et al., 2011; Rammohan et al., 2012; Comi et al., 2013; Leist et al., 2014; Freedman et al., 2017; Giovannoni, 2017; Giovannoni et al., 2018). The long-lasting therapeutic effect of the drug is believed to be related to transient reversible reductions in lymphocytes and certain lymphocyte subsets (Giovannoni, 2017; Baker et al., 2017; Comi et al., 2019; Leist and Weissert, 2009; Stuve et al., 2019; Wiendl, 2017).

Long-term safety data are of particular interest for any newly approved treatment in MS and cladribine tablets 3.5 mg/kg is uniquely supported by long-term safety data from the clinical development program. Indeed, the safety profile of cladribine tablets 3.5 mg/kg has been well characterized with prior publication of interim integrated safety data from two earlier data cut-offs (cumulative to February 2015 and May 2017, respectively), including interim data from the long-running safety registry, PREMIERE (Cook et al., 2019; Cook et al., 2018).

Previous safety updates have shown that, in general, there was no increase in the risk of infections with cladribine tablets 3.5 mg/kg versus placebo during the clinical development program, except for herpes zoster (Cook et al., 2019). Periods of severe lymphopenia ($<0.5 \times 10^9$ cells/L) were associated with an increased frequency of infections, but the pattern of infections was not different to that in an overall group receiving cladribine tablets 3.5 mg/kg (Cook et al., 2019). In the CLARITY trial, there was a numerical imbalance in the malignancy rate with cladribine tablets relative to placebo (Giovannoni et al., 2010), but the rate in the overall clinical program for cladribine in MS was not significantly increased compared to placebo-treated patients and with no increase in the incidence of malignancies over time in cladribine-treated patients being apparent (Cook et al., 2019).

Here we provide the final report on the integrated analysis of the safety profile of cladribine tablets 3.5 mg/kg from the clinical development program, including final data from the PREMIERE registry.

2. Methods

2.1. Patients – monotherapy oral cohort

In this final report from the clinical development program, safety data for cladribine tablets 3.5 mg/kg and 5.25 mg/kg from the three Phase III studies, CLARITY, CLARITY Extension and ORACLE-MS, and the completed PREMIERE registry were combined (**Fig. 1**). Cladribine tablets 5.25 mg/kg over 2 years is not an approved dose; data for patients who received this dose in the clinical development program are shown in the supplementary tables.

Full methodology for the integrated analysis has been described in detail previously (Cook et al., 2019). Briefly: CLARITY (NCT00213135) was a 96-week, Phase III, double-blind, randomized, placebo-controlled, parallel-group, multicenter study evaluating the safety and efficacy of cladribine tablets with cumulative doses of 3.5 and 5.25 mg/kg in patients with relapsing-remitting MS (RRMS) (Giovannoni et al., 2010). CLARITY Extension (NCT00641537) was a 96-week, Phase IIIb, double-blind, randomized, parallel-group, multicenter, extension study that evaluated the safety and efficacy of cladribine tablets for an additional 2 years beyond the CLARITY study, with and without further

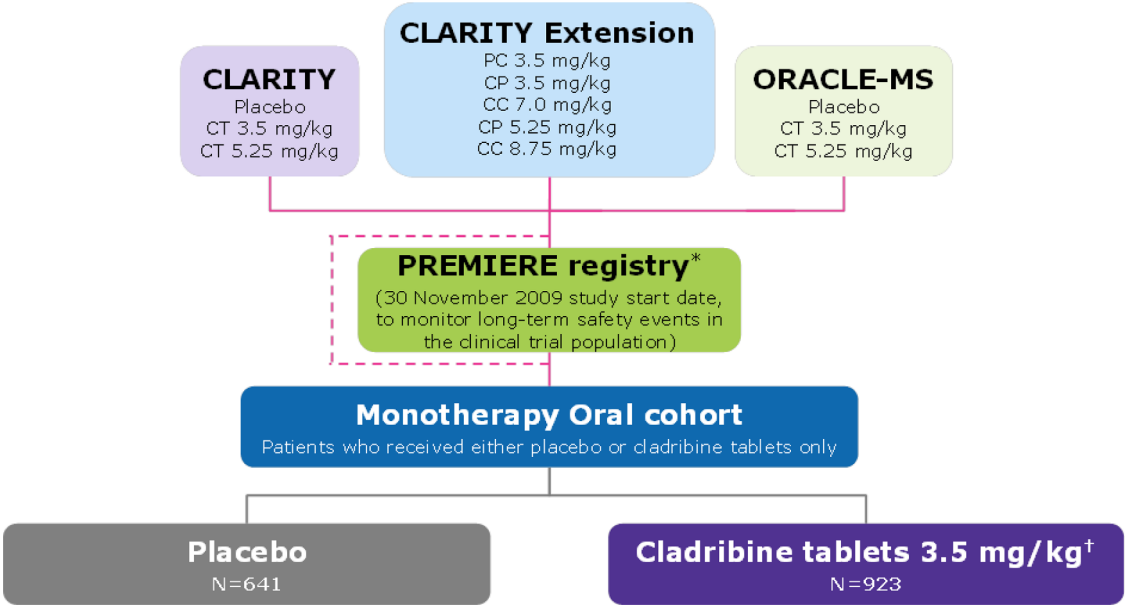


Fig. 1. Overview of patients treated with cladribine tablets 3.5 mg/kg or placebo in the Monotherapy Oral cohort.
*Patients with prior enrolment into selected clinical trials with cladribine tablets were eligible to enter PREMIERE once participation in the clinical trial had ended, but not all clinical trial participants were included in the registry as indicated by the dotted line.
†The Monotherapy Oral cohort also contained a cladribine tablets (CT) 5.25 mg/kg treatment group; data not shown. 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 to CT (i.e. in CLARITY Extension [Ext]), then their data became part of the placebo group. Patients who switched treatment from placebo to CT in subsequent studies/periods had their time on placebo censored at the time of the switch. Patients who switched treatment from placebo to CT 3.5 mg/kg had their time on CT 3.5 mg/kg initiated at the time of switching. Patients who were treated with CT 3.5 mg/kg in CLARITY and were then re-exposed to CT 3.5 mg/kg in a subsequent study/period (i.e. in CLARITY Ext) had their time on CT 3.5 mg/kg censored at the time of re-exposure.
CP 3.5 mg/kg, CT 3.5 mg/kg in CLARITY followed by placebo in CLARITY Ext; CP 5.25 mg/kg, CT 5.25 mg/kg in CLARITY followed by placebo in CLARITY Ext; CC 7 mg/kg, CT 3.5 mg/kg in CLARITY followed by CT 3.5 mg/kg in CLARITY Ext; CC 8.75 mg/kg, CT 5.25 mg/kg in CLARITY followed by CT 3.5 mg/kg in CLARITY Ext; PC 3.5 mg/kg, placebo in CLARITY followed by CT 3.5 mg/kg in CLARITY Ext.

treatment (Giovannoni et al., 2018). ORACLE-MS (NCT00725985) was a 96-week Phase III, double-blind, randomized, placebo-controlled, multicenter study that evaluated the safety and efficacy of cladribine tablets at cumulative doses of 3.5 and 5.25 mg/kg over 2 years in patients with a first clinical demyelinating event (Leist et al., 2014; Freedman et al., 2017). The PREMIERE registry (NCT01013350), which ran from November 2009 to October 2018, was a prospective, observational, long-term safety study of patients who had participated in at least one of the four cladribine tablets interventional clinical trials (CLARITY (Giovannoni et al., 2010), CLARITY Extension (Giovannoni et al., 2018), ORACLE-MS (Leist et al., 2014), or ONWARD (Montalban et al., 2018)).

Patients with prior enrolment into these trials were eligible, with written informed consent, to enter PREMIERE once participation in the respective clinical trial had ended. The objective of the PREMIERE registry was to monitor long-term safety in the clinical trial population in order to better characterize the potential safety risks of oral cladribine tablets 3.5 mg/kg. The total duration of follow-up was 8 years after the patients' first enrolment into a clinical trial or until October 2018, whichever occurred first. No investigational product or placebo was administered during the PREMIERE registry period.

The Monotherapy Oral cohort represents the primary cohort that evaluated the safety of cladribine tablets 3.5 mg/kg as monotherapy with long-term follow-up data, and was used for all safety analyses described in this report. Patients from the ONWARD study were excluded from the Monotherapy Oral cohort, because patients received IFN-beta treatment in addition to cladribine tablets.

2.2. Analysis of adverse events and serious adverse events

All safety analyses were performed using the 'as treated principle', as described in a prior safety publication (Cook et al., 2019), with patients who switched from placebo to cladribine tablets 3.5 mg/kg having their time on placebo censored at the time of switch. Patients who were treated with cladribine tablets 3.5 mg/kg in CLARITY and were re-exposed 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. All integrated analyses were performed using SAS® Software version 9.2 or later.

Adverse events (AEs) and Medical Histories in all studies were recoded using the Medical Dictionary of Regulatory Activities (MedDRA) v20.0. As previously described (Cook et al., 2019), treatment emergent AEs (TEAEs) were defined as AEs absent prior to treatment that occurred on or after day 1 during the treatment and observation period. Assessments of AEs mainly used observation-adjusted incidence rates (Adj-AE). Adjusted AE incidence per 100 patient-years (Adj-AE per 100 PY) were calculated as the time-adjusted AE incidence rate; this can be interpreted as the average number of events expected to occur 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). Serious AEs were defined as AEs resulting in death, that were life-threatening, required inpatient hospitalization, resulted in congenital anomaly or birth defect, or were otherwise considered as medically important.

2.3. Serious adverse events of special interest

Lymphopenia is an expected AE due to the mode of action of cladribine, which causes selective, transient lymphocyte reduction. Consequently, lymphopenia-associated immunosuppression and reduction of cell-mediated immunity raises potential concerns about an increase in the incidence of infections or malignancies. Three categories of AEs – lymphopenia, infections, and malignancies – were therefore pre-defined as serious AEs of special interest (AESI). With regard to malignancies, standardized incidence ratios (SIRs) were calculated in relation to the matched GLOBOCAN 2012 reference population (GLOBOCAN, 2012). Risk differences (cladribine tablets versus placebo) were presented with corresponding two-sided 95% confidence intervals (CIs) on Adj-AE per 100 PY, estimated by the Miettinen and Nurminen method unless otherwise specified (Miettinen and Nurminen, 1985).

Data are also presented for the system organ class 'skin and subcutaneous tissue disorders' and for the preferred term 'rash, generalized', as part of the AESI evaluation.

3. Results

3.1. Patient characteristics

This final integrated safety analysis for the Monotherapy Oral cohort included 923 patients who received cladribine tablets 3.5 mg/kg and 641 patients who received placebo. Patient characteristics were generally balanced between the two groups (**Table 1**). Approximately two-thirds of patients were women and the mean age was similar between those receiving placebo and those receiving cladribine tablets 3.5 mg/kg. The number of patients exposed to cladribine tablets 3.5 mg/kg was larger and they had a longer average time period of follow up compared to those who received placebo, reflective of the fact that placebo-treated patients from CLARITY may have received cladribine tablets 3.5 mg/kg in CLARITY Extension.

3.2. Serious TEAEs

The incidence of serious TEAEs is summarized in **Table 2**. Overall the reported number of serious TEAEs was higher in the cladribine tablets 3.5 mg/kg group (133/923 [14.4%] patients with at least 1 serious TEAE) versus the placebo group (68/641 [10.6%] patients with at least 1 serious TEAE). The corresponding incidence of serious TEAEs was 3.80 and 3.05 per 100 PY, respectively. There were no cases of

Table 1
Characteristics of patients included in the Monotherapy Oral cohort from the cladribine tablets clinical development program.

	Placebo (N = 641)	Cladribine tablets 3.5 mg/kg (N = 923)
Patient-years[a]	2421.5	3936.7
Time on study, years;[a] mean (SD)	3.79 (2.67)	4.28 (2.54)
Time on study, ≥96 weeks (~2 years), *n* (%)	493 (76.9)	784 (84.9)
Time on study, ≥192 weeks (~4 years), *n* (%)	204 (31.8)	431 (46.7)
Time on study, ≥432 weeks (~9 years), *n* (%)	18 (2.8)	26 (2.8)
Age, years;[b] mean (SD) Median Range	37.15 (9.83) 36.53 18.1–64.2	37.84 (10.48) 37.62 18.2–66.1
Age ≤40 years,[b] *n* (%)	396 (61.8)	540 (58.5)
Age >40 years,[b] *n* (%)	245 (38.2)	383 (41.5)
Female, *n* (%)	424 (66.1)	612 (66.3)
Prior treatment with DMD, *n* (%)	131 (20.4)	184 (19.9)

DMD, disease-modifying drug; SD, standard deviation.
[a] Cumulative to October 2018.
[b] As reported at first dosing date.

progressive multifocal leukoencephalopathy in the cladribine clinical development program for MS.

3.3. Serious adverse events of special interest

3.3.1. Lymphopenia

In the cladribine tablets 3.5 mg/kg group, 4/923 patients had lymphopenia classified as a serious TEAE, resulting in an Adj-AE of 0.10 per 100 PY (Table 3). There were no serious lymphopenia events in the placebo group.

3.3.2. Infections

The overall incidence of infection and infestations is shown in Table 3. The rate of serious infections and infestations was 2.5% (23/923 patients) in the cladribine tablets 3.5 mg/kg group and 1.6% (10/641 patients) in the placebo group, resulting in an Adj-AE of 0.60 and 0.42 per 100 PY, respectively.

In the cladribine tablets 3.5 mg/kg group, 2/923 patients (0.2%) experienced serious herpes zoster, resulting in an Adj-AE of 0.05 per 100 PY. There were no cases of serious herpes zoster in the placebo group. There was one case each of tuberculosis and pulmonary tuberculosis in the cladribine tablets 3.5 mg/kg group classified as serious. There was no obvious pattern of increase in other serious respiratory infections. Incidence of AESI severe infections, AESI opportunistic infections, and AESI herpetic infections for the Monotherapy Oral cohort are summarized in Table 4.

The incidence of severe infections was low in both the cladribine tablets 3.5 mg/kg group (Adj-AE of 0.76 per 100 PY) and the placebo group (Adj-AE of 0.81 per 100 PY). The incidence of opportunistic infections was an Adj-AE of 0.31 per 100 PY for cladribine tablets 3.5 mg/kg and 0.17 per 100 PY for placebo; the difference was driven primarily by fungal infections. Fungal infections were mainly mucocutaneous and there were no systemic infections such as candida sepsis. AESI herpetic infections occurred more frequently in the cladribine tablets 3.5 mg/kg group (driven primarily by herpes zoster, followed by oral herpes and herpes simplex). Herpes zoster occurred more frequently during periods of Grade 3 or 4 lymphopenia ($<0.5 \times 10^9$ cells/L) with an Adj-AE of 4.15 versus 0.64 per 100 PY. There were no cases of serious disseminated herpes zoster attributed to treatment with cladribine tablets. The incidence of pneumonia was similar in both groups, with an Adj-AE of 0.15 per 100 PY for cladribine tablets 3.5 mg/kg versus 0.12 per 100 PY for placebo.

3.3.3. Malignancy

Overall, there was a numerical imbalance in malignancy incidence between cladribine tablets 3.5 mg/kg and placebo with an Adj-AE of 0.26 and 0.12 per 100 PY, respectively (difference not statistically significant); this was based on 10 cases of malignant tumors in the cladribine tablets 3.5 mg/kg group with an exposure of 3918.9 patient years, versus 3 cases in the placebo group with an exposure of 2414.8 patient years (Table 5). There was no clustering of malignancies of any type i.e. different cancer types were only reported once in cladribine tablets 3.5 mg/kg patients (with the exception of malignant melanoma, which was reported in two patients). Timing of diagnosis of malignancy versus start of study drug ranged from 169 to 1853 days (Table 5). No increase in malignancies commonly associated with immunosuppression was observed.

Compared to the matched GLOBOCAN reference population (GLOBOCAN, 2012), the rate of malignancies observed with cladribine tablets 3.5 mg/kg in the final integrated safety analysis was not different from the expected rate in the matched reference population (SIR, 0.88; 95% CI, 0.44–1.69; Fig. 2). The corresponding SIR for placebo was 0.42 (95% CI, 0.12–1.33). The GLOBOCAN database does not include data on non-melanoma skin cancers (NMSCs); however, there was no increase in NMSCs compared with placebo and no increase compared with key epidemiological data from Denmark (Norgaard et al., 2019).

Table 2
Frequently reported serious* TEAEs (Adj-AE per 100 PY of ≥0.10; excluding TEAEs of special interest) in the Monotherapy Oral cohort from the cladribine tablets clinical development program.

	Placebo (N = 641)			Cladribine tablets 3.5 mg/kg (N = 923)		
System organ class Preferred term	n	Total PY	Adj-AE per 100 PY	n	Total PY	Adj-AE per 100 PY
At least 1 serious TEAE	68	2226.2	3.05	133	3498.1	3.80
Cardiac disorders	6	2410.4	0.25	7	3917.4	0.18
Endocrine disorders	4	2411.2	0.17	3	3929.3	0.08
Thyroid mass	3	2412.2	0.12	1	3934.5	0.03
Eye disorders	3	2418.2	0.12	3	3927.8	0.08
Gastrointestinal disorders	3	2403.0	0.12	11	3895.9	0.28
General disorders and administration site conditions	3	2413.0	0.12	6	3930.4	0.15
Hepatobiliary disorders	3	2413.0	0.12	6	3930.1	0.15
Injury, poisoning and procedural complications	5	2397.6	0.21	17	3885.1	0.44
Investigations	6	2402.7	0.25	14	3883.7	0.36
Blood creatine phosphokinase increased	4	2418.1	0.17	7	3908.0	0.18
Musculoskeletal and connective tissue disorders	3	2415.7	0.12	6	3919.2	0.15
Nervous system disorders	6	2411.7	0.25	12	3896.1	0.31
Pregnancy, puerperium and perinatal conditions	7	2407.1	0.29	9	3901.8	0.23
Abortion spontaneous†	3	2416.6	0.12	2	3935.1	0.05
Pregnancy	3	2413.5	0.12	1	3930.5	0.03
Psychiatric disorders	5	2411.7	0.21	4	3929.5	0.10
Renal and urinary disorders	3	2414.1	0.12	3	3927.0	0.08
Reproductive system and breast disorders	3	2411.6	0.12	8	3897.1	0.21
Respiratory, thoracic and mediastinal disorders	4	2410.3	0.17	8	3903.6	0.20
Surgical and medical procedures	3	2408.4	0.12	6	3915.6	0.15

*Serious was defined as resultant in death, life-threatening, required inpatient hospitalization, congenital anomaly or birth defect, or was otherwise considered as medically important.
†Spontaneous miscarriage.
The Medical Dictionary for Regulatory Activities (MedDRA) v20.0 was used for adverse event coding.
Adj-AE per 100 PY, adjusted adverse events incidences per 100 patient-years; AESI, adverse events of special interest; PY, patient-years; TEAE, treatment emergent adverse events.

Table 3
Serious* TEAEs of special interest in the Monotherapy Oral cohort from the cladribine tablets clinical development program. For AESI malignancies, see Table 5.

System organ class Preferred term	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
Blood and lymphatic system disorders	0	2421.5	0	10	3912.7	0.26
Lymphopenia	0	2421.5	0	4	3925.4	0.10
Infections and infestations	10	2395.8	0.42	23	3857.2	0.60
Anal abscess	0	2421.5	0	1	3932.5	0.03
Appendicitis	2	2419.0	0.08	1	3930.8	0.03
Breast abscess	0	2421.5	0	1	3933.2	0.03
Chronic hepatitis C	1	2414.9	0.04	0	3936.7	0
Chronic sinusitis	1	2419.6	0.04	0	3936.7	0
Diverticulitis	0	2421.5	0	1	3936.5	0.03
Erysipelas	1	2414.5	0.04	0	3936.7	0
Gastroenteritis	0	2421.5	0	1	3933.2	0.03
Herpes zoster	0	2421.5	0	2	3929.7	0.05
Infection	0	2421.5	0	1	3936.6	0.03
Influenza	0	2421.5	0	1	3935.2	0.03
Myocarditis bacterial	1	2419.7	0.04	0	3936.7	0
Peritonitis	0	2421.5	0	1	3929.8	0.03
Pilonidal cyst	0	2421.5	0	1	3929.0	0.03
Pneumonia	3	2415.2	0.12	6	3907.4	0.15
Pulmonary tuberculosis	0	2421.5	0	1	3933.6	0.03
Pyelonephritis	0	2421.5	0	2	3927.2	0.05
Salpingo-oophoritis	0	2421.5	0	1	3934.6	0.03
Subcutaneous abscess	0	2421.5	0	1	3936.4	0.03
Tuberculosis	0	2421.5	0	1	3936.7	0.03
Urethral abscess	1	2421.4	0.04	0	3936.7	0
Urinary tract infection	1	2419.9	0.04	4	3923.4	0.10
Skin and subcutaneous tissue disorders	1	2420.5	0.04	3	3934.5	0.08
Rash generalized	0	2421.5	0	1	3936.6	0.03

The Medical Dictionary for Regulatory Activities (MedDRA) v20.0 was used for adverse event coding.
Adj-AE per 100 PY, adjusted adverse events incidences per 100 patient-years; AESI, adverse events of special interest; PY, patient-years; TEAE, treatment emergent adverse events.
*Serious was defined as resultant in death, life-threatening, required inpatient hospitalization, congenital anomaly or birth defect, or was otherwise considered as medically important.

There was no increase in the risk of malignancy over time with cladribine tablets 3.5 kg/mg (Fig. 3). The malignancy rate for cladribine tablets 3.5 kg/mg during years 1–4 was an Adj-AE of 0.29 per 100 PY and from year 5 onwards was 0.17 per 100 PY. In contrast, the malignancy rate in the placebo group during years 1–4 was an Adj-AE of 0.06 per 100 PY, but higher from year 5 onwards at 0.29 per 100 PY; however, the overall number of events was small.

3.3.4. Skin and subcutaneous tissue disorders

In the cladribine tablets 3.5 mg/kg group, 1/923 patients had generalized rash classified as a serious TEAE, resulting in an Adj-AE of 0.03 per 100 PY (Table 3). There were no reports of serious generalized rash in the placebo group.

4. Discussion

This analysis marks the final update to the safety data from the clinical development program for the approved dose of cladribine tablets 3.5 mg/kg and includes the finalized data from the end of the PREMIERE registry (cumulative to October 2018). Overall, results confirm the low level of serious TEAEs associated with cladribine tablets 3.5 mg/kg in patients with RRMS. The results of this updated analysis are therefore consistent with those from previously published analyses, cumulative to February 2015 and May 2017, respectively (Cook et al., 2019; Cook et al., 2018).

Table 4
Summary of AESI infections and infestations (severe infection, opportunistic infection, and herpetic infection; Adj-AE of ≥0.05 in any group) for the Monotherapy Oral cohort from the cladribine tablets clinical development program.

	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
Severe infection	19	2358.8	0.81	29	3829.1	0.76
Appendicitis	2	2419.0	0.08	1	3930.8	0.03
Gastroenteritis	0	2421.5	0	2	3925.3	0.05
Herpes zoster	1	2415.6	0.04	3	3928.1	0.08
Pneumonia	4	2412.6	0.17	6	3907.4	0.15
Pyelonephritis	0	2421.5	0	2	3927.2	0.05
Sinusitis	0	2421.5	0	2	3935.0	0.05
Urinary tract infection	2	2418.9	0.08	4	3923.4	0.10
Opportunistic infection	4	2411.0	0.17	12	3874.8	0.31
Fungal infection	2	2418.9	0.08	9	3891.0	0.23
Herpetic infection	19	2343.1	0.81	60	3737.0	1.61
Herpes simplex	2	2412.2	0.08	5	3916.9	0.13
Herpes virus infection	1	2416.1	0.04	4	3920.9	0.10
Herpes zoster	4	2397.1	0.17	28	3855.8	0.73
Oral herpes	10	2387.5	0.42	20	3868.4	0.52
Varicella	2	2416.1	0.08	3	3926.7	0.08

Adj-AE per 100 PY, adjusted adverse events incidences per 100 patient-years; AESI, adverse events of special interest.
AESI Severe infection is a custom grouping defined by any serious or severe event belonging to the MedDRA system organ class Infections and infestations.
AESI Opportunistic infection is based on respective lists available in the context of HIV
infections. It includes MedDRA preferred terms associated to viral, fungal, protozoal and bacterial
infections which is different from the data presented in the previous manuscript by Cook et al. 2019.[14]
AESI Herpetic infection is defined by any events from MedDRA HLT = Herpes viral infections.

The current summary focuses on the Monotherapy Oral cohort, as this is in line with the approved dose of cladribine tablets (3.5 mg/kg). This analysis does not present in detail data from the previously reported 'All Exposed' cohort of patients from the clinical development program because that cohort includes data for other cladribine formulations and dosing regimens (Cook et al., 2019). The final results from the All Exposed cohort are, however, in line with the earlier report, and at the final cut-off included 1976 patients who received cladribine with an exposure of 9854.7 patient years and 802 who received placebo with an exposure of 2781.8 patient years.

As for previous reports, the safety data analyzed here are presented as observation-adjusted incidence rates per 100 patient years of exposure and follow-up time to account for different follow-up times in the treatment arms (Cook et al., 2019; Cook et al., 2018). This is relevant for this long-term update because the observation time for the placebo group is only about one third that of the cladribine tablets 3.5 mg/kg group, and the comparison would not be meaningful if presented as percentages.

The adjusted incidence rates of serious TEAEs decreased with the longer follow-up in this report. In addition, no new major safety findings were identified, and there were no new/significant adverse events emerging during long-term follow-up after treatment with cladribine

Table 5
Number of AESI malignancies, timing of events, incidence rates, risk difference, and risk ratio for the Monotherapy Oral cohort from the cladribine tablets clinical development program.

	Placebo (N = 641)		Cladribine tablets 3.5 mg/kg (N = 923)	
	n	Days at onset*	n	Days at onset*
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Basal cell carcinoma	1	1972	1	1317
Bile duct adenocarcinoma	0	0	1	926
Bowen's disease	0	0	1	465
Breast cancer	0	0	1	1711
Cervical carcinoma stage 0	2	1871, 993	0	0
Malignant melanoma	0	0	2	1204, 419
Ovarian cancer	0	0	1	169
Pancreatic carcinoma metastatic	0	0	1	509
Papillary thyroid cancer	0	0	1	582
Rectal cancer	0	0	1	1853
	n	Total PY	N	Total PY
n/PY at risk	3	2414.8	10	3918.9
Incidence per 100 PY		0.12		0.26
Risk difference per 100 PY			0.1309	
95% CI of risk difference per 100 PY†			−0.1304, 0.3645	
Risk ratio			2.0540	
95% CI of risk ratio‡			0.5653, 7.4632	

AESI, adverse events of special interest; CI, confidence interval; PY, patient-years.
*(Imputed AE onset date - first study drug date) + 1.
†CI computed using the Miettinen and Nurminen method.
‡CI computed with the Wald method for the number of patients with events using a Poisson regression model with fixed effect for treatment group and with log of time at risk as an offset. When the observed rate is zero, the lower limit is set to zero and the exact formula is used for the upper limit.

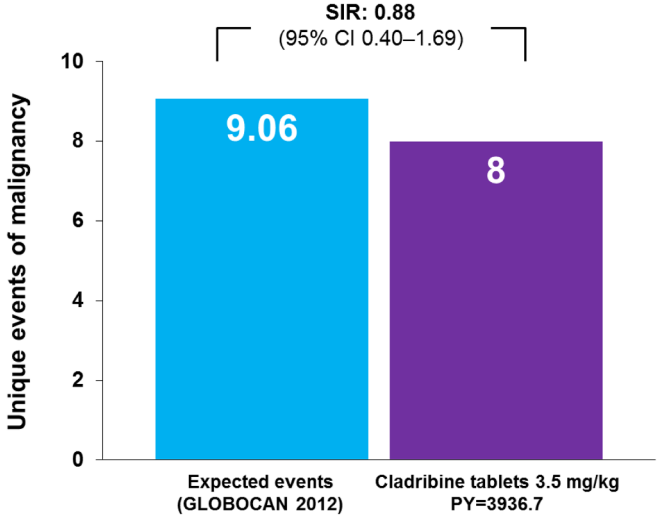


Fig. 2. Malignancy incidence for cladribine tablets 3.5 mg/kg compared with a matched GLOBOCAN reference population.
CI, confidence interval; PY, patient-years; SIR, standardized incidence ratio (calculated against the matched GLOBOCAN reference population, excluding non-melanoma skin cancer due to inconsistent reporting).

tablets 3.5 mg/kg. It is also worth noting that despite the risk of secondary autoimmune disorders with some MS treatments (Genzyme Therapeutics Ltd. 2018), there were no secondary autoimmune disorders reported in the Monotherapy Oral cohort. This finding provides further evidence that the mechanism of action of cladribine tablets has minimal deleterious impact on long-term immune function (Giovannoni, 2017; Baker et al., 2017; Comi et al., 2019; Leist and Weissert, 2009; Stuve et al., 2019; Wiendl, 2017).

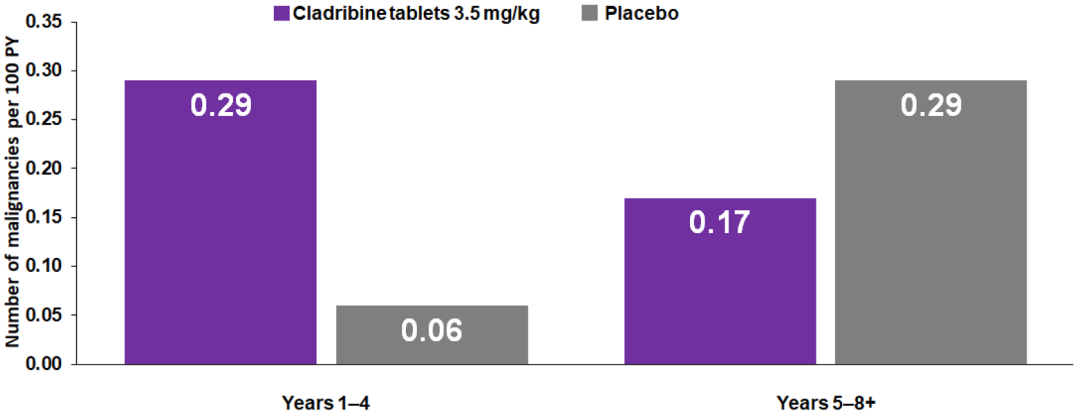
There was no increased risk for infections with the exception of serious herpes zoster, which showed an increased incidence among cladribine tablets 3.5 mg/kg recipients versus placebo (Adj-AE of 0.05 per 100 PY in the cladribine tablets 3.5 mg/kg group versus no cases in the placebo group). Previous analyses have shown that frequency of infections is related to occurrences of severe lymphopenia ($<0.5 \times 10^9$ cells/L) (Giovannoni et al., 2010; Giovannoni et al., 2018; Cook et al., 2019). In patients treated with cladribine tablets 3.5 mg/kg, Grade 4 lymphopenia ($<0.2 \times 10^9$ cells/L) occurred in <1% of patients, but the nature of their infections was not different to that observed in the overall patient group (Giovannoni et al., 2010; Giovannoni et al., 2018; Cook et al., 2019). It was clear, however, that herpes zoster occurred more frequently during periods of severe lymphopenia than in periods without severe lymphopenia. A time-to-event analysis reported from the February 2015 cut off suggested that the risk of herpes zoster or herpetic infections may be temporally linked to the dosing period with cladribine tablets 3.5 mg/kg in years 1 and 2, but the low number of overall events did not allow definitive conclusions to be drawn (Cook et al., 2019). Known risk factors for herpes zoster include family history, being female, white, and, of particular relevance to patients taking cladribine tablets, immunosuppression (Kawai and Yawn, 2017). There was one case each of tuberculosis and pulmonary tuberculosis in the cladribine tablets 3.5 mg/kg group classified as serious. However, these cases were seen in patients who received their first doses of cladribine tablets 3.5 mg/kg prior to the implementation of mandatory tuberculosis screening. There was no obvious pattern of increase in other serious respiratory infections.

The incidence rate of serious or severe infections was low in the cladribine tablets 3.5 mg/kg group and no relevant differences versus placebo were observed at the preferred term level. This reflects infection screening requirements in the clinical program, which are also reflected in the prescribing information for cladribine tablets (Groves et al., 2013).

A numerical imbalance in the incidence of malignancy was noted between cladribine tablets 3.5 mg/kg and placebo, with an Adj-AE of 0.26 and 0.12 per 100 PY, respectively; however, the difference was not statistically significant. The duration from first intake of study drug until a malignancy diagnosis was highly variable and there was no increase in the incidence of malignancies over time. The incidence of malignancies was higher during the first 4 years of the program than for the subsequent 4 years, for cladribine tablets 3.5 mg/kg. Surprisingly, the incidence of malignancies in the placebo group was lower than expected during the first 4 years of the program and higher than expected in the subsequent 4 years. To determine the effect of dose on malignancy, an analysis using data from the All Exposed and Monotherapy Oral cohorts for the 3.5 mg/kg and 5.25 mg/kg groups was previously undertaken (Cook et al., 2011). This analysis showed that, overall, there was no clear evidence of a dose effect of cladribine on malignancy risk in patients with MS based on more than 9500 patient years of cladribine exposure (Cook et al., 2011).

The observation-adjusted incidence of malignancies is lower than the previous reports (Cook et al., 2019; Cook et al., 2018), and is explained by the number of cases not changing in this update and there being a longer follow up. Similarly, when compared to the reference GLOBOCAN population, the SIR for cladribine tablets 3.5 mg/kg in this final analysis (0.88) was lower than in the previous publication (0.97) (Cook et al., 2019). In both GLOBOCAN population analyses, the rate of malignancies with cladribine tablets 3.5 mg/kg was similar to the expected rate from the matched reference population and the rate of malignancies with placebo was lower than expected overall.

In summary, this final report consolidates over 8 years of safety data from the clinical development program of cladribine tablets and identified no new major safety findings. These integrated analyses



	Cladribine tablets 3.5 mg/kg	Placebo	Cladribine tablets 3.5 mg/kg	Placebo
Patients with events	8	1	2	2
Time at risk, years	2768.2	1727.0	1160.1	692.0

Fig. 3. Risk of malignancy over time for cladribine tablets 3.5 mg/kg and placebo.

demonstrate the favorable AE profile and safety for cladribine tablets 3.5 mg/kg monotherapy in patients with RRMS, which are now well characterized over long-term use. It is unique for a disease-modifying drug to have such long-term safety data available soon after approval. Furthermore, there are two on-going post-approval safety studies (CLARION [EU PAS Register number, EUPAS24484] and CLEAR [EU PAS Register number, EUPAS25027]) that are looking at the long-term overall safety of patients exposed to prescribed cladribine tablets as well as pregnancy outcomes. Results from these studies will be reported periodically.

Author statement

We confirm that all authors made substantial contributions to the concept and design, or analysis and interpretation of data, and to the drafting of the manuscript or revising it critically for important intellectual content. In addition, all authors provided final approval of the manuscript.

Funding

Merck KGaA, Darmstadt, Germany provided financial support for the conduct of the research and preparation of the article. Merck KGaA, Darmstadt, Germany, in collaboration with all authors, was involved in the study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article.

Data availability statement

Any requests for data by qualified scientific and medical researchers for legitimate research purposes will be subject to Merck KGaA's Data Sharing Policy. All requests should be submitted in writing to Merck KGaA'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 KGaA 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 KGaA will endeavor to gain agreement to share data in response to requests.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

TL has received consultancy fees or clinical research grants from Acorda, Bayer, Biogen, Daiichi, EMD Serono, Novartis, ONO, Pfizer, and Teva Neuroscience.

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

GC has received consulting fees from Bayer Schering, Biogen, Genentech/Roche, Merck KGaA (Darmstadt, Germany), Novartis, Receptos, Sanofi-Aventis, and Teva Pharmaceutical Industries Ltd; lecture fees from Bayer Schering, Biogen, Merck KGaA (Darmstadt, Germany), Novartis, Sanofi-Aventis, Serono Symposia International Foundation, and Teva Pharmaceutical Industries Ltd; and trial grant support from Bayer Schering, Biogen, Genentech/Roche, Merck KGaA (Darmstadt, Germany), Novartis, Receptos, Sanofi-Aventis, and Teva Pharmaceutical Industries Ltd.

XM has received speaking honoraria and travel expenses for scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past 3 years with Actelion, Alexion, Bayer, Biogen, Celgene, EMD Serono, EXCEMED, Genzyme, MedDay, Merck KGaA (Darmstadt, Germany) MSIF, Nervgen, NMSS, Novartis, Roche, Sanofi-Genzyme, Teva Pharmaceutical, and TG Therapeutics.

GG has received speaker honoraria and consulting fees from AbbVie, Actelion, Atara Bio, Almirall, Bayer Schering Pharma, Biogen, Celgene, FivePrime, GlaxoSmithKline, GW Pharma, Ironwood, Merck & Co., Merck KGaA (Darmstadt, Germany), Novartis, Pfizer Inc., Protein Discovery Laboratories, Roche, Sanofi-Genzyme, Teva Pharmaceutical Industries Ltd, UCB, and Vertex Pharmaceuticals; and has received research support unrelated to this study from Biogen, Ironwood, Merck & Co., Novartis and Takeda.

AN is an employee of Merck KGaA, Darmstadt, Germany.

DD is an employee of EMD Serono Research & Development Institute, Inc., Billerica, USA, a business of Merck KGaA, Darmstadt, Germany.

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

Acknowledgments

This study was supported by Merck KGaA, Darmstadt, Germany. The authors would like to thank patients and their families, investigators, co-investigators, and the study teams at each of the participating centers and at Merck KGaA, Darmstadt, Germany. Medical writing assistance was provided by Mark O'Connor and Ella Palmer of inScience Communications, Springer Healthcare Ltd, UK, and was funded by 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.2020.102572.

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