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Clinical trial

# Effect of cladribine tablets on lymphocyte reduction and repopulation dynamics in patients with relapsing multiple sclerosis

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ABSTRACT

*Background:* Immune reconstitution therapies (IRT) for patients with multiple sclerosis are used for short, intermittent treatment periods to induce immune resetting and allow subsequent treatment-free periods. Cladribine tablets are postulated to be an IRT that causes selective and transient reductions in $CD19^+$ B cells and T cells, followed by reconstitution of adaptive immune function.

*Objective:* To characterize long-term lymphocyte count changes in pooled data from the 2-year CLARITY and subsequent 2-year CLARITY Extension studies, and the PREMIERE registry (Long-term CLARITY cohort).

*Methods:* Data from patients randomized to placebo ($n = 435$) or cladribine tablets 10 mg (MAVENCLAD®; 3.5 mg/kg cumulative dose over 2 years, referred to as cladribine tablets 3.5 mg/kg; $n = 685$) in CLARITY or CLARITY Extension, including time spent in the PREMIERE registry were pooled to provide long-term follow-up data. The study investigated absolute lymphocyte counts (ALC) up to 312 weeks and B and T cell subsets up to 240 weeks after the first dose, in patients receiving placebo or cladribine tablets 3.5 mg/kg administered as two short (4 or 5 days) weekly treatments at the start of months 1 and 2 in each treatment year, followed by no further active treatment.

*Results:* Treatment with cladribine tablets 3.5 mg/kg resulted in selective reductions in B and T lymphocytes. Lymphocyte recovery began soon after treatment in each of years 1 and 2. Median ALC recovered to the normal range and $CD19^+$ B cells recovered to threshold values by week 84, approximately 30 weeks after the last dose of cladribine tablets in year 2. Median $CD4^+$ T cell counts recovered to threshold values by week 96 (approximately 43 weeks after the last dose of cladribine tablets in year 2). Median $CD8^+$ cell counts never dropped below the threshold value.

*Conclusion:* These results show the dynamics of lymphocyte count changes following treatment with cladribine tablets 3.5 mg/kg. The immune cell repopulation results provide further evidence that cladribine tablets may represent a form of IRT.

The CLARITY study: NCT00213135.
The CLARITY Extension study: NCT00641537.
The PREMIERE registry: NCT01013350.

## 1. Introduction

Immune reconstitution therapies (IRT) for patients with multiple sclerosis (MS) are used for short, intermittent treatment periods to induce immune resetting and allow treatment-free periods (Giovannoni, 2017; Wiendl, 2017). Cladribine tablets 10 mg (MAVENCLAD®) are thought to be an IRT that causes selective and transient reductions in $CD19^+$ B cells and T cells, followed by reconstitution of the adaptive immune system (Giovannoni, 2017; Wiendl, 2017). Cladribine is a prodrug which is phosphorylated intracellularly to its active

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form, 2-chlorodeoxyadenosine triphosphate (Cd-ATP), by deoxycytidine kinase, and Cd-ATP is degraded by 5′-nucleotidase (Beutler, 1992; Comi et al., 2013). Lymphocytes contain a higher deoxycytidine kinase to 5′-nucleotidase activity ratio than other cells types, which means Cd-ATP accumulates to high levels in lymphocytes, and thus causes the selective reduction of these cells (Beutler, 1992; Comi et al., 2013).

Cladribine tablets have been approved for the treatment of highly active relapsing MS (RMS) in the European Union (EU) (Merck Serono Europe Limited, 2017). Cladribine 10 mg tablets are given as a cumulative oral dose of 3.5 mg/kg over 2 years (henceforth referred to as cladribine tablets 3.5 mg/kg), administered as 1 treatment course of 1.75 mg/kg per year in each of the 2 years. In the EU Summary of Product Characteristics (SmPC), criteria for initiating and continuing treatment with cladribine tablets are based on absolute lymphocyte count (ALC) being normal (Common Terminology Criteria for Adverse Events; [CTCAE] Grade 0) before treatment in the first year and $\geq 0.8 \times 10^9$ cells/L (CTCAE Grade 1 or 0) before treatment in the second year.

In the Phase III CLARITY study, a cumulative dose of cladribine tablets 3.5 mg/kg given over 2 years was shown to significantly reduce relapse rates, risk of disability progression, and magnetic resonance imaging (MRI) measures of disease activity vs. placebo in patients with RMS (Giovannoni et al., 2010). In patients who subsequently received placebo in the CLARITY Extension study, clinical benefits were maintained for a further 2 years with no additional active treatment, demonstrating the durable efficacy of cladribine tablets 3.5 mg/kg (Giovannoni et al., 2017). The safety profile of cladribine tablets 3.5 mg/kg has been broadly described in a companion safety publication *Multiple Sclerosis and Related Disorders* (Cook et al., 2018). Data presented in the companion publication are primarily from a pooled analysis of Phase III clinical trials for patients with early to more advanced RMS receiving the approved dose of cladribine tablets 3.5 mg/kg as monotherapy (the CLARITY, CLARITY Extension and ORACLE-MS studies, plus follow-up in the PREMIERE registry; the 'Monotherapy Oral' cohort). The companion manuscript also includes data from an All Exposed cohort of patients who were exposed to cladribine by any route of administration or at higher doses during the clinical development program in multiple sclerosis (MS). This cohort pooled patients from the same trials used for the Monotherapy Oral cohort, together with patients from the ONWARD study of cladribine tablets with concomitant interferon (IFN)-β therapy, plus 5 trials of parenteral cladribine in patients with MS (Scripps-A, -B and -C, MS-Scripps and MS-001).

Lymphopenia is an anticipated effect of cladribine treatment, due to its pharmacological properties and selective depletion of lymphocytes; in clinical trials, lymphopenia was reported more frequently as an adverse event (AE) for cladribine tablets 3.5 mg/kg than for placebo (adjusted AE incidences per 100 patient years 7.94 vs. 1.06 for placebo) (Cook et al., 2018). Monitoring of lymphopenia during treatment with disease modifying drugs (DMDs) for MS is relevant because of the potential for an associated increase in risk of infections. A *post-hoc* analysis of the Monotherapy Oral cohort reported in the companion publication examined infectious AEs occurring during periods of severe (Grade 3 or 4) lymphopenia in patients treated with cladribine tablets 3.5 mg/kg. 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.

Interactions between the innate and adaptive immune system are involved in the prevention of cancer development, and patients with profound immunosuppression (e.g., patients with HIV-AIDS, idiopathic $CD4^+$ lymphopenia, or transplant patients who are treated with strongly immunosuppressive therapy) have an increased cancer risk (Oliveira Cobucci et al., 2012; Ahmad et al., 2013). Lymphoproliferative disorders and non-melanoma skin cancer (NMSC) occur frequently in patients with profound immunosuppression (Didona et al., 2018; McPherson and Kirk, 2017; Perez et al., 2017). In the integrated safety analysis of clinical trials with cladribine in patients with MS, no lymphoproliferative disorders and no increased risk of NMSC vs. placebo were observed in either the Monotherapy Oral or All Exposed cohorts (Cook et al., 2018).

In order to examine the incidence of and recovery from lymphopenia during treatment with cladribine tablets in detail, here, we report data from a pooled patient cohort most suitable for analysis of lymphocyte count dynamics over time. Data from RMS patients in CLARITY (Giovannoni et al., 2010), CLARITY Extension (Giovannoni et al., 2017) and the PREMIERE registry ('Long-term CLARITY' cohort) allowed long-term follow-up of the lymphocyte counts. In patients receiving placebo or cladribine tablets (3.5 mg/kg cumulative dose) administered as two short (4 or 5 days) weekly treatments at the start of months 1 and 2 in each treatment year, followed by no further active treatment, ALC was analyzed up to 312 weeks, and B and T cell subsets up to 240 weeks after the first administered dose.

## 2. Methods

### 2.1. Long-term CLARITY cohort

Longitudinal lymphocyte data are provided by pooled analyses of double-blind studies in which patients with RMS were treated with placebo or cladribine tablets 3.5 mg/kg as monotherapy (the current approved dose) (Merck Serono Europe Limited, 2017). Data were pooled from 2 Phase III studies that involved treatment with cladribine tablets 3.5 mg/kg; CLARITY (Giovannoni et al., 2010) and CLARITY Extension (Giovannoni et al., 2017), and in patients from these studies followed up in the Prospective Observational Long-term Safety Registry of Multiple Sclerosis Patients Who Have Participated in Cladribine Clinical Trials (PREMIERE registry).

Patients randomized to cladribine tablets 3.5 mg/kg in CLARITY were pooled with those who received cladribine tablets 3.5 mg/kg for the first time in CLARITY Extension (following placebo in CLARITY). Baseline was defined as the date of treatment initiation with cladribine tablets 3.5 mg/kg in both trials. After 2 years' treatment with cladribine tablets, no further active treatment was administered in these patients. Patients randomized to placebo in CLARITY were assigned to cladribine tablets 3.5 mg/kg in CLARITY Extension for ethical reasons. Therefore, clinical trial data for the placebo group in this report are limited to 2 years (plus follow-up in the PREMIERE registry). It is of note that this includes the bridging intervals in treatment between CLARITY and CLARITY Extension and prior to the PREMIERE registry, periods during which the lymphocyte counts of patients were not monitored. The limited number of patients who received IFN-β as rescue therapy ($n = 11$; <3% of patients treated with cladribine tablets 3.5 mg/kg) were not excluded or censored.

### 2.2. Analyses

ALC was measured as part of a complete blood count performed by a central laboratory with $CD19^+$ B cells, $CD4^+$ T cells, and $CD8^+$ T cells quantified in a subset of patients using flow cytometry as part of a lymphocyte surface marker analysis. Threshold counts were defined as $0.10 \times 10^9$, $0.35 \times 10^9$, and $0.20 \times 10^9$ cells/L for $CD19^+$ B cells, and $CD4^+$ and $CD8^+$ T cells, respectively. Thresholds for $CD19^+$ B cells and $CD8^+$ T cells were chosen based on values used in previous studies of disease modifying drugs (DMDs) for multiple sclerosis (Hill-Cawthorne et al., 2012), and the threshold for $CD4^+$ T cells was chosen based on the value used for initiating antiretroviral therapy in patients with human immunodeficiency virus, below which there is an increased risk of infection (Vitoria et al., 2013). All analyses were performed using SAS® Software version 9.2 or later.

## 3. Results

In the Long-term CLARITY cohort, patients exposed to cladribine tablets 3.5 mg/kg ($n = 685$) were more numerous than patients

**Table 1**
Baseline demographics and clinical characteristics for patients included in the Long-term CLARITY cohort.

| | Placebo (*N* = 435) | Cladribine tablets 3.5 mg/kg (*N* = 685) |
|---|---|---|
| Time on study in weeks, mean (SD) | 168.67 (116.70) | 205.13 (117.48) |
| Time on study ≥24 weeks (~6 months), n (%) | 418 (96.1) | 669 (97.7) |
| Time on study ≥48 weeks (~1 year), n (%) | 399 (91.7) | 656 (95.8) |
| Time on study ≥96 weeks (~2 years), n (%) | 337 (77.5) | 597 (87.2) |
| Time on study ≥192 weeks (~4 years), n (%) | 91 (20.9) | 286 (41.8) |
| Time on study ≥384 weeks (~8 years), n (%) | 60 (13.8) | 93 (13.6) |
| Age (years),[a] Mean (SD) | 38.7 (9.9) | 38.2 (10.1) |
| Median | 38.0 | 38.0 |
| Min; Max | 18; 64 | 18; 65 |
| Age ≤40 years,[a] n (%) | 247 (56.8) | 400 (58.4) |
| Age >40 years,[a] n (%) | 188 (43.2) | 285 (41.6) |
| Female, n (%) | 286 (65.7) | 462 (67.4) |
| Prior treatment with DMD, n (%) | 131 (30.1) | 184 (26.9) |
| Disease duration in years, mean (SD) | 8.91 (7.39) | 7.90 (6.91) |

DMD, disease modifying drug; SD, standard deviation.
*a Baseline was defined as the start of the core studies for these parameters.

receiving only placebo ($n = 435$) and were followed over a longer period (Table 1). Patient demographics were similar between the cladribine tablets 3.5 mg/kg and placebo treatment groups (Table 1).

### 3.1. Absolute lymphocyte counts

Median ALC over time is shown in Fig. 1. In the cladribine tablets 3.5 mg/kg group, ALC fell initially following treatment and lymphocyte recovery began soon afterwards in year 1 and year 2. During year 1, median (interquartile range) ALC reached a nadir of $1.00 \times 10^9$ cells/L (0.80; 1.30) at 2 months after start of treatment in the group treated with cladribine tablets 3.5 mg/kg. At the end of year 1 (48 weeks), median ALC had increased to $1.21 \times 10^9$ cells/L (0.95; 1.50). During year 2, median ALC in the group treated with cladribine tablets 3.5 mg/kg reached a nadir of $0.81 \times 10^9$ cells/L (0.60; 1.04) at 55 weeks (i.e. week 7 in year 2). Median ALC returned to the normal range ($1.00 \times 10^9$ cells/L [0.76; 1.30]) (Territo, 2019) by 84 weeks (week 36 in year 2), increasing to $1.03 \times 10^9$ cells/L (0.80; 1.30) at the end of year 2 (96 weeks). Median ALC returned to the normal range in 75% of patients treated with cladribine tablets 3.5 mg/kg by 144 weeks. In patients randomized to placebo, median ALC was between $1.69 \times 10^9$ and $1.95 \times 10^9$ cells/L over the 4-year period (low numbers of patients were available for analysis).

### 3.2. B lymphocyte counts

Median $CD19^+$ B cell counts were $0.205 \times 10^9$ cells/L (0.143; 0.265) at baseline in patients treated with cladribine tablets 3.5 mg/kg (Fig. 2). After treatment in year 1, $CD19^+$ B cells reached a nadir at 2 months (median $0.018 \times 10^9$ cells/L [0.010; 0.035]), and then increased rapidly. After treatment in year 2, a nadir was observed at 52 weeks (median $0.031 \times 10^9$ cells/L [0.020; 0.058]). $CD19^+$ B cells then rapidly recovered, reaching the threshold of $0.100 \times 10^9$ cells/L by 84 weeks, and continuing to improve thereafter. Recovery to threshold values occurred approximately 30 weeks after the last dose of cladribine tablets in each treatment year. In patients randomized to placebo, median $CD19^+$ B cell counts were between $0.193 \times 10^9$ and $0.225 \times 10^9$ cells/L.

### 3.3. T lymphocyte counts

Median $CD4^+$ T-cell counts in patients treated with cladribine tablets 3.5 mg/kg were $0.851 \times 10^9$ cells/L (0.652; 1.051) at baseline (Fig. 3). After treatment in year 1, median $CD4^+$ T cells reached a nadir at 4 months ($0.385 \times 10^9$ cells/L [0.292; 0.578]) and then gradually increased. Median $CD4^+$ T cells reached a nadir after treatment in year 2 at 60 weeks ($0.292 \times 10^9$ cells/L [0.212; 0.429]). Values then gradually recovered, exceeding the threshold of $0.350 \times 10^9$ cells/L by 96 weeks (around 43 weeks after the last dose of cladribine tablets in year 2), and continuing to improve thereafter. In patients randomized to placebo, median $CD4^+$ T cell counts were between $0.746 \times 10^9$ and $0.822 \times 10^9$ cells/L.

Median $CD8^+$ T cell counts were $0.378 \times 10^9$ cells/L (0.283; 0.540) at baseline in patients treated with cladribine tablets 3.5 mg/kg (Fig. 4). $CD8^+$ T cells reached a nadir in year 1 at 4 months (median $0.239 \times 10^9$ cells/L [0.146; 0.384]), and then gradually increased. A nadir in year 2 was reached at 72 weeks (median $0.232 \times 10^9$ cells/L [0.155; 0.335]). Median $CD8^+$ T cells recovered after treatment and never dropped below the lower limit of normal of $0.200 \times 10^9$ cells/L at any time in the 240-week observation period. In patients randomized to placebo, median $CD8^+$ T cell counts were between $0.373 \times 10^9$ and $0.424 \times 10^9$ cells/L.

The decrease in $CD8^+$ T cells after treatment with cladribine tablets 3.5 mg/kg was less pronounced compared with the decrease in $CD4^+$ T cells, and the recovery was faster, meaning that the $CD4^+/CD8^+$ ratio was temporarily decreased.

## 4. Discussion

Due to its established mode of action, treatment with cladribine tablets results in selective reduction of B and T lymphocytes. Lymphocyte reductions following treatment with cladribine tablets are relatively gradual, in comparison with the very rapid reductions seen after treatment with monoclonal antibodies with a cytolytic mode of action (Baker et al., 2017a; Montalban et al., 2017). Consequently, treatment with cladribine tablets does not require comedication (Merck Serono Europe Limited, 2017) to alleviate the cell lysis syndrome that occurs with monoclonal antibodies. Preclinical data shows that cladribine can also reduce the secretion of inflammatory cytokines and chemokines in human and murine dendritic cells (Kraus et al., 2014).

Recovery of lymphocyte counts begins soon after treatment with cladribine tablets in year 1 and year 2. Furthermore, median ALC and $CD19^+$ B cell counts recovered to threshold values by approximately 30 weeks after the last dose of cladribine tablets in year 2. Median B cell counts stabilized upon returning to baseline and did not exceed baseline levels, potentially explaining the lack of secondary B cell autoimmunity which has been observed after treatment with other DMDs for MS. (Baker et al., 2017b) Median $CD4^+$ T cell counts recovered to threshold values by approximately 43 weeks after the last dose of cladribine tablets in year 2, and median $CD8^+$ cell counts never dropped below the threshold value. Effects of treatment with cladribine tablets on other lymphocyte subsets is also of interest – more detailed immunophenotyping, including extensive data from the ORACLE-MS study, will be the subject of a separate report.

In the CLARITY and CLARITY Extension studies, Grade 3 lymphopenia (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). The EU SmPC for cladribine tablets states that the treatment course in year 2 can be delayed for up to 6 months to allow for recovery of lymphocytes, but if recovery takes more than 6 months, the patient should not receive further treatment (Merck Serono Europe Limited, 2017). When the ALC-based treatment scenarios were investigated in a clinical trial simulation based on the CLARITY study in order to assess the impact of postponing treatment in the second year on the risk of severe lymphopenia (Terranova et al., 2018), it was predicted that by allowing a 6 month delay, ~99% of patients would be eligible for the second year

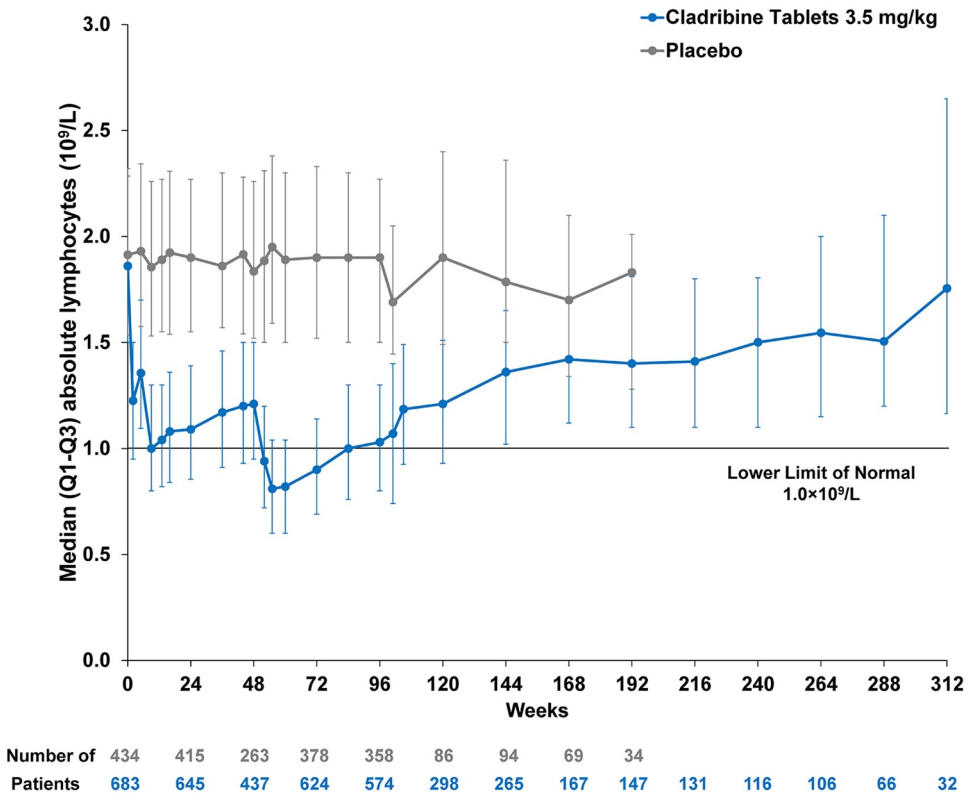


**Fig. 1.** Median absolute lymphocyte counts over time in the cladribine tablets 3.5 mg/kg and placebo groups. Visits with sample size ≥30 are displayed. Reproduced with permission from Giovannoni (2017).

course having recovered to ALC $\geq 0.8 \times 10^9$ cells/L. The ALC-based treatment guidelines were employed throughout the ORACLE-MS study, and the median duration of Grade ≥3 lymphopenia was reduced from 5.4 months (as observed in CLARITY) to 3.0 months (as observed in ORACLE-MS) and the incidence of Grade 4 lymphopenia was 0.4% (European Medicines Agency, 2017). A *post-hoc* analysis of patients

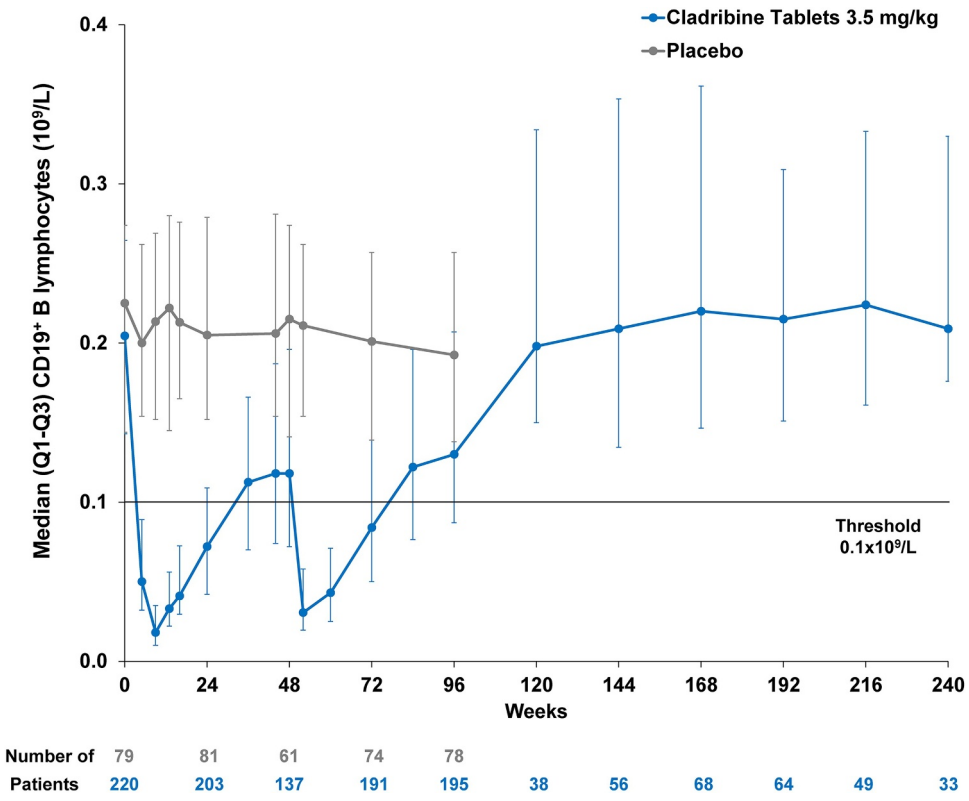


**Fig. 2.** Median $CD19^+$ B lymphocyte counts over time in the cladribine tablets 3.5 mg/kg and placebo groups. Visits with sample size ≥30 are displayed.

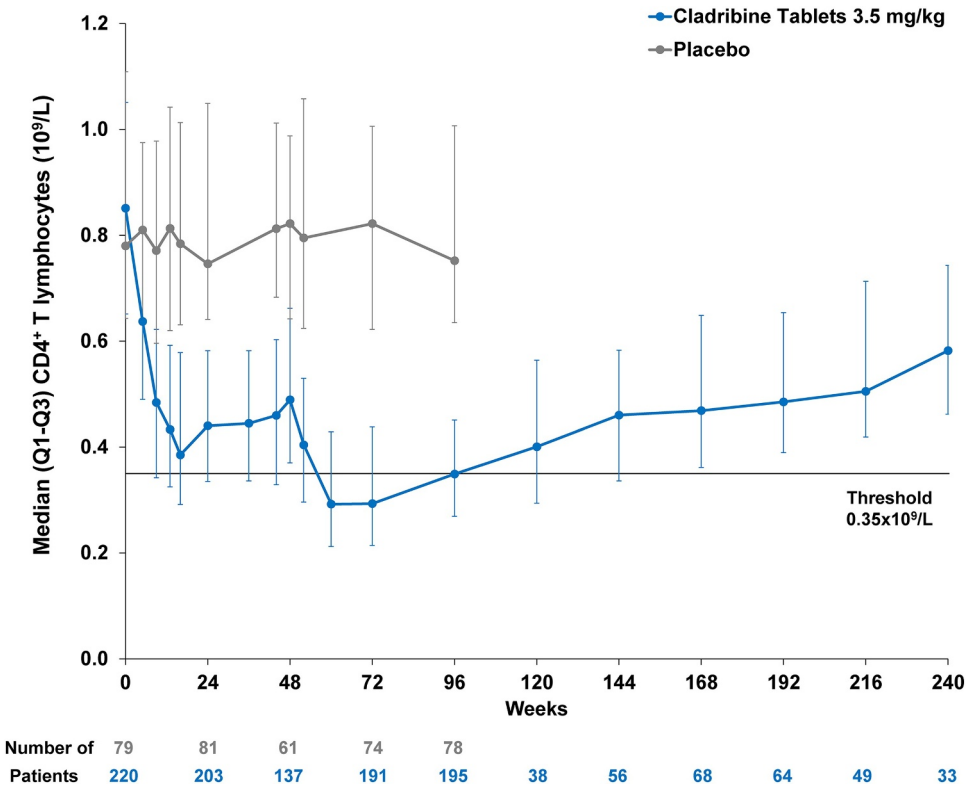


**Fig. 3.** Median $CD4^+$ T lymphocyte counts over time in the cladribine tablets 3.5 mg/kg and placebo groups. Visits with sample size ≥30 are displayed.

randomized to cladribine tablets 3.5 mg/kg in CLARITY followed by cladribine tablets 3.5 mg/kg in CLARITY Extension ($n$ = 186), i.e. a cumulative dose of 7 mg/kg over 4 years, is reported in the Supplementary Information. Additional courses of treatment did not numerically decrease the proportion of patients recovering to Grade 0–1 lymphopenia at the end of each treatment year, in patients that met ALC-based treatment criteria at the start of each treatment year (Supplementary Fig. 1A).

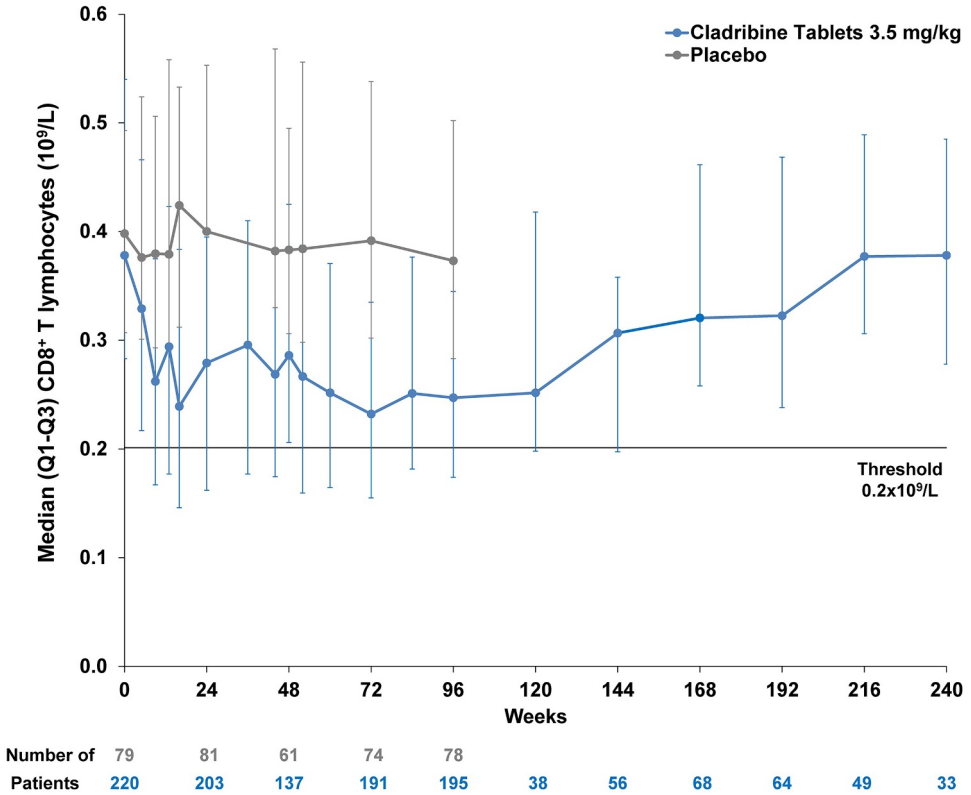


**Fig. 4.** Median $CD8^+$ T lymphocyte counts over time in the cladribine tablets 3.5 mg/kg and placebo groups. Visits with sample size ≥30 are displayed.

The current study focused on lymphocyte counts in peripheral blood. A key unresolved question with cladribine tablets in the treatment of RMS is the effect on tissue-infiltrating lymphocytes, particularly in the central nervous system (CNS). Unlike monoclonal antibodies, which appear to have limited access to the CNS, cladribine is a small molecule with detectable distribution into tissues, including the CNS (Saven et al., 1996; Kearns et al., 1994). While it has been proposed that the concentrations of cladribine achieved in the CNS may be capable of causing apoptosis in lymphoblasts (Freyer et al., 2015), it is not yet clear how the concentrations achieved in the CNS with the tablet formulation and in therapeutic doses appropriate for RMS would directly affect adaptive immune cell function in the brain and spinal cord. Nevertheless, treatment with cladribine tablets 3.5 mg/kg followed by placebo demonstrated a durable reduction of clinical and MRI markers of inflammatory disease activity characteristic of MS. There was no rebound of clinical or MRI activity even after recovery of ALC (Giovannoni et al., 2017; Comi et al., 2018). This suggests some form of qualitative change in the adaptive immune response after treatment with cladribine tablets.

Recent studies of cladribine tablets treatment effects on innate immune cells (Soelberg Sorensen et al., 2017) showed that up to 4 years after initiating treatment with cladribine tablets 3.5 mg/kg median neutrophil counts never dropped below the normal range. Median monocyte counts were $0.40 \times 10^9$ cells/L at baseline and ranged from $0.34–0.36 \times 10^9$ cells/L at the end of years 2–4. Median natural killer cells were transiently reduced after treatment with cladribine tablets, with an early decrease followed by rapid recovery with cell count ranges largely overlapping those of placebo-treated patients (Stuve et al., 2017).

The companion publication describing an integrated safety analysis (Cook et al., 2018) provides more detailed information on AEs related to lymphopenia from the Monotherapy Oral cohort. Although severe lymphopenia in patients treated with cladribine tablets 3.5 mg/kg resulted in an increased frequency of infections, the infectious AE profile observed during periods of Grade 3 and 4 lymphopenia did not differ from that seen outside of these periods. Opportunistic infections that could be life-threatening (e.g., progressive multifocal leukoencephalopathy, cryptococcosis, toxoplasmosis, pneumocystis jirovecii pneumonia, or cytomegalovirus infection) were not observed in patients treated with cladribine tablets. Infections commonly observed with IRTs that impact innate immunity (e.g., listeriosis) (Holmoy et al., 2017) were not observed with cladribine tablets. The results reported in this publication, and the apparently minimal or no impact on certain aspects of innate immune function, including monocyte and neutrophil counts and infectious AE profile, support the notion that cladribine tablets selectively and transiently reduce adaptive immune cells while preserving certain components of the innate immune system.

## Conclusion

The current study shows that total lymphocytes, $CD19^+$ B cells and $CD8^+$ T cells recovered to their respective normal ranges after treatment with cladribine tablets 3.5 mg/kg over a time period when efficacy was otherwise shown to be maintained, with no resurgence of clinical or MRI disease activity (Giovannoni et al., 2016). $CD4^+$ levels recovered more slowly, but without evidence of the opportunistic infection risk that would be expected from long-term T cell reductions. The immune cell repopulation results presented here provide further evidence that cladribine tablets may represent a form of IRT.

## Role of the funding source

Merck KGaA, Darmstadt, Germany provided financial support for the conduct of this research and preparation of the article. The sponsor participated in the study design, collection, analysis and interpretation of the data; in the writing of the report and in the decision to submit the article for publication.

## Conflict of interest

GC has received consulting fees from Novartis, Teva Pharmaceutical Industries Ltd., Sanofi-Aventis, Merck, Receptos, Biogen Idec, Genentech-Roche, and Bayer Schering; lecture fees from Novartis, Teva Pharmaceutical Ind. Ltd., Sanofi-Aventis, Merck, Biogen Dompè, Bayer Schering, and Serono Symposia International Foundation; and trial grant support from Novartis, Teva Pharmaceutical Ind. Ltd., Sanofi-Aventis, Receptos, Biogen Idec, Genentech-Roche, Merck, Biogen Dompè, and Bayer Schering.

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

GG has received speaker honoraria and consulting fees from Abbvie, Actelion, Atara Bio, Almirall, Bayer Schering Pharma, Biogen Idec, FivePrime, GlaxoSmithKline, GW Pharma, Merck & Co., Merck KGaA, 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 & Co., Novartis, and Ironwood.

PR has received honoraria for lectures/steering committee meetings from Merck, Biogen Idec, Bayer Schering Pharma, Boehringer-Ingelheim, Sanofi-Aventis, Genzyme, Novartis, Teva Pharmaceutical Industries, and Serono Symposia International Foundation.

PSS has served on advisory boards for Biogen, Merck KGaA, Novartis, Teva, MedDay Pharmaceuticals, and GSK; on steering committees or independent data monitoring boards in trials sponsored by Merck KGaA, Teva, GSK, and Novartis; has received speaker honoraria from Biogen Idec, Merck KGaA, Teva, Sanofi-Aventis, Genzyme, and Novartis. His department has received research support from Biogen, Merck KGaA, Teva, Novartis, Roche, and Genzyme.

PV has received honoraria or consulting fees from Biogen, Sanofi-Genzyme, Bayer, Novartis, Merck KGaA, Celgene, Roche and Almirall; and research support from Biogen, Sanofi-Genzyme, Bayer, and Merck KGaA.

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

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

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

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2019.01.038.

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