Rates of Lymphopenia in Years 1–4 in Patients with Relapsing Multiple Sclerosis Treated Annually with Cladribine Tablets

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INTRODUCTION

- The efficacy of cladribine tablets 3.5 mg/kg in patients with relapsing multiple sclerosis was demonstrated in the two-year CLARITY study[1] and maintained in the two-year CLARITY Extension study.[2]
- The most common adverse event in both studies was lymphopenia, consistent with the mechanism of action of cladribine tablets.[1,2]
- Rates of lymphopenia were assessed in patients who had been treated according to treatment guidelines[3] in CLARITY and CLARITY Extension.

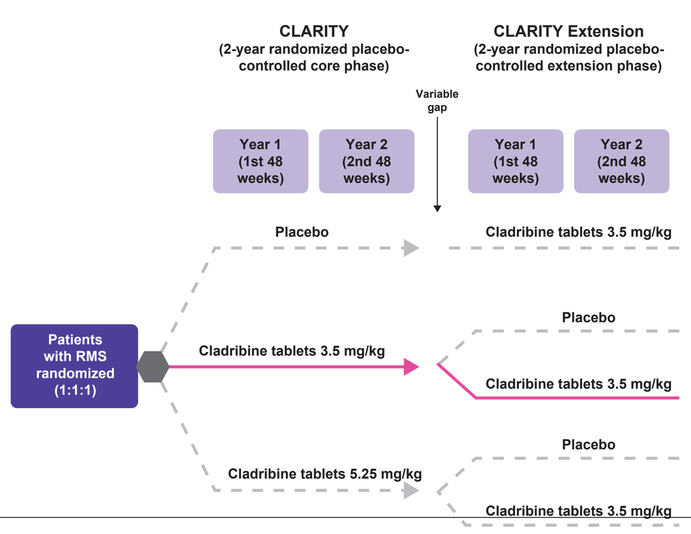
OBJECTIVE

- To evaluate whether lymphopenia persists following annual treatment with cladribine tablets (up to four years' treatment; 7 mg/kg cumulative dose).

METHODS

- The study designs for CLARITY and CLARITY Extension are shown in **Figure 1**.
- The subgroup included in this analysis comprised patients that were randomized to cladribine tablets 3.5 mg/kg in the CLARITY study followed by re-randomization to a further course of cladribine tablets 3.5 mg/kg in CLARITY Extension (n = 186), i.e. patients that received a cumulative dose of 7 mg/kg over four years.
- Lymphopenia was graded with the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0.[4]
- Patients included in the analysis were required to have Grade 0 lymphopenia (≥ 1.0 × 10^9 cells/L) before the first course of treatment with cladribine tablets 3.5 mg/kg and Grade 0 or 1 lymphopenia (≥ 0.8 × 10^9 cells/L) prior to administration of all subsequent courses in Years 2, 3, and 4.[3]

Figure 1. CLARITY and CLARITY Extension Study Designs



RMS, relapsing multiple sclerosis.

RESULTS

Patients

- Demographics and disease characteristics of patients randomized to cladribine tablets 3.5 mg/kg in CLARITY and re-randomized to cladribine tablets 3.5 mg/kg in CLARITY Extension are shown in **Table 1**.
- The majority of patients who were treated annually with cladribine tablets over four years were female, white, and aged 40 years or younger at the baseline of CLARITY, similar to the overall cladribine tablets 3.5 mg/kg arm of CLARITY.[1]

Table 1. Baseline* Demographics and Clinical Characteristics of Patients Included in the Analysis

Patients Treated Annually with Cladribine Tablets for up to 4 Years (n = 186)	
Age, years	37.9 (10.4)
Age ≤ 40 years, n (%)	116 (62.4)
Age > 40 years, n (%)	70 (37.6)
Female, n (%)	124 (66.7)
White, n (%)	181 (97.3)
Disease duration, years	7.75 (7.10)
EDSS score	2.68 (1.18)
Prior treatment with DMD, n (%)	43 (23.1)

* Baseline of CLARITY.
Data are mean (SD) unless otherwise stated.
DMD, disease modifying drug; **EDSS**, Expanded Disability Status Scale.

Lymphopenia

- In patients randomized to cladribine tablets 3.5 mg/kg and re-randomized to a further course of cladribine tablets 3.5 mg/kg (n = 186), the following patients were eligible to receive treatment in CLARITY and CLARITY Extension:
  - 176 patients had Grade 0 lymphopenia at the start of CLARITY
  - 167 patients had Grade 0 or 1 lymphopenia at the start of CLARITY Extension.
- No patients had Grade 4 lymphopenia at the end of any of the 4 treatment years (**Table 2**).
- Grade 3 lymphopenia was uncommon at the end of each treatment year, only occurring in 2 patients at the end of Year 2 (**Table 2**).

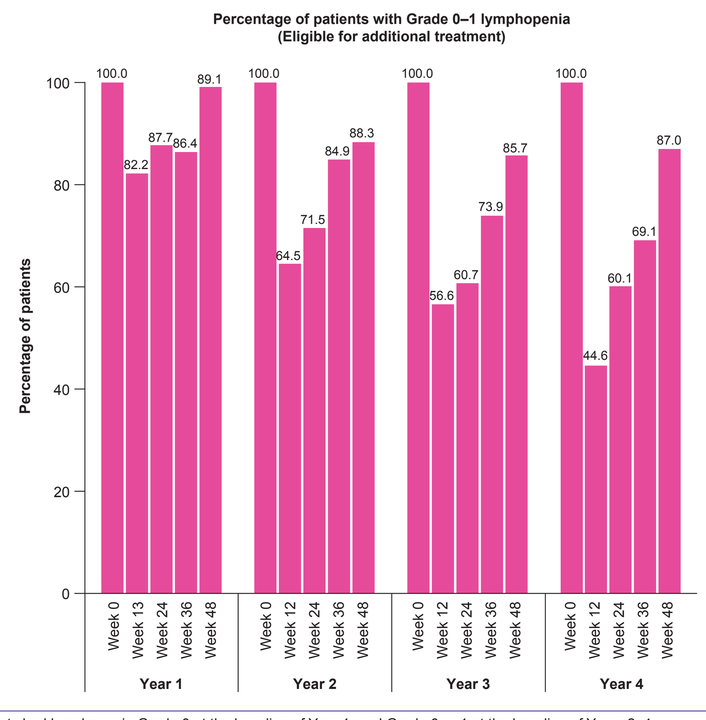
Table 2. Lymphopenia by Grade in Patients that Received Cladribine Tablets Annually for up to 4 Years

	CLARITY				CLARITY Extension			
	Year 1		Year 2		Year 3		Year 4	
	Start	End	Start	End	Start	End	Start	End
Patients*	176	175	161	154	167	161	136	123
Lymphopenia Grade†								
0	176	119	122	97	134	86	85	59
1	0	37	39	39	33	52	51	48
2	0	19	0	16	0	23	0	16
3	0	0	0	2	0	0	0	0
4	0	0	0	0	0	0	0	0

Data shown are number of patients.
* Patients had lymphopenia Grade 0 at the baseline of Year 1, and Grade 0 or 1 at the baseline of Years 2–4; end of year values are the number of patients with laboratory values.
† Lymphopenia graded by the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0;[4] **Grade 0**: ≥ 1.0 × 10^9 cells/L; **Grade 1**: 0.8–< 1.0 × 10^9 cells/L; **Grade 2**: 0.5–< 0.8 × 10^9 cells/L; **Grade 3**: 0.2–< 0.5 × 10^9 cells/L; **Grade 4**: < 0.2 × 10^9 cells/L.

- By Week 48 in each of Years 1, 2, 3, and 4, Grade 0 or 1 lymphopenia was observed in 86–89% of patients and these patients therefore met the lymphocyte criteria for treatment with cladribine tablets (**Figure 2**).

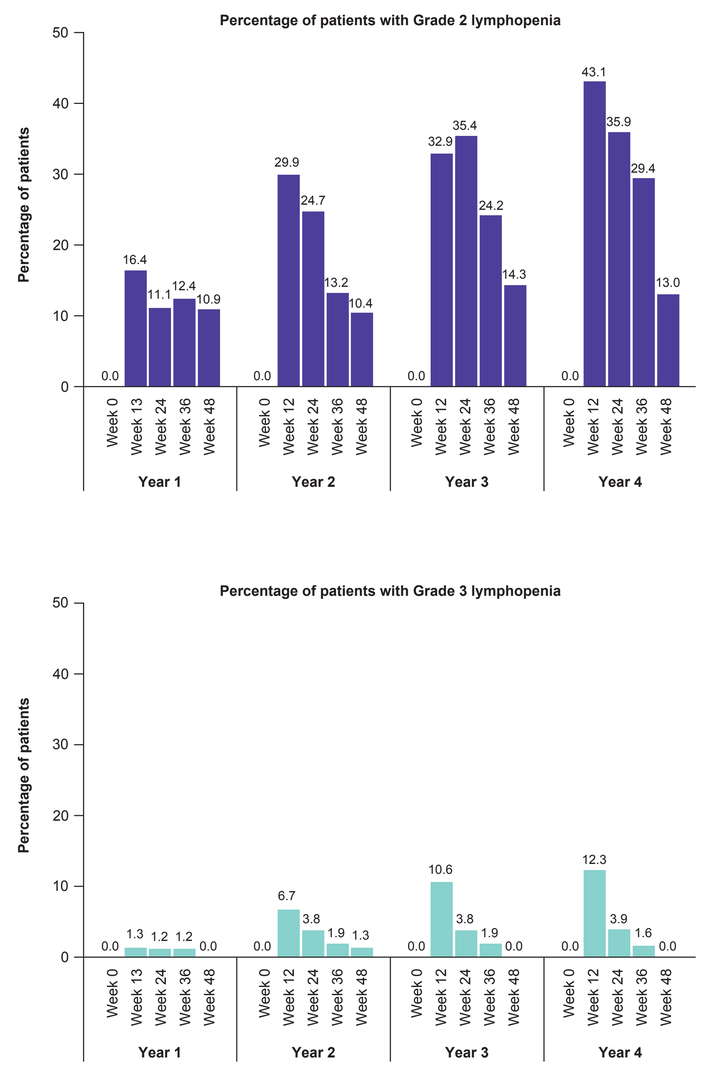
Figure 2. Grade 0–1 Lymphopenia Over Time in Patients Who Received Cladribine Tablets for up to 4 Years



Patients had lymphopenia Grade 0 at the baseline of Year 1, and Grade 0 or 1 at the baseline of Years 2–4.
Percentages were calculated as a proportion of all patients with laboratory values at each time point.
Lymphopenia was graded by the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0;[4] **Grade 0**: ≥ 1.0 × 10^9 cells/L; **Grade 1**: 0.8–< 1.0 × 10^9 cells/L; **Grade 2**: 0.5–< 0.8 × 10^9 cells/L; **Grade 3**: 0.2–< 0.5 × 10^9 cells/L; **Grade 4**: < 0.2 × 10^9 cells/L.

- By Week 13 in Year 1 and Week 12 in Years 2, 3, and 4, up to 43.1% and 12.3% of patients developed Grade 2 and Grade 3 lymphopenia, respectively (**Figure 3**).

Figure 3. Grade 2 or Grade 3 Lymphopenia Over Time in Patients Who Received Cladribine Tablets for up to 4 Years



Patients had lymphopenia Grade 0 at the baseline of Year 1, and Grade 0 or 1 at the baseline of Years 2–4.
Percentages were calculated as a proportion of all patients with laboratory values at each time point.
Lymphopenia was graded by the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0;[4] **Grade 0**: ≥ 1.0 × 10^9 cells/L; **Grade 1**: 0.8–< 1.0 × 10^9 cells/L; **Grade 2**: 0.5–< 0.8 × 10^9 cells/L; **Grade 3**: 0.2–< 0.5 × 10^9 cells/L; **Grade 4**: < 0.2 × 10^9 cells/L.

- In this subgroup treated according to treatment guidelines, additional annual courses of treatment with cladribine tablets, up to a cumulative dose of 7 mg/kg, did not numerically decrease the proportion of patients recovering to Grade 0–1 lymphopenia at the end of each treatment year (**Figure 2**).
- In this subgroup of patients who received cladribine tablets 3.5 mg/kg in CLARITY and a further course of cladribine tablets 3.5 mg/kg in Years 3 and 4 of CLARITY Extension, according to the treatment guidelines (a cumulative dose of 7 mg/kg), a total of 1.7% of patients experienced ≥ 1 episode of Grade 4 lymphopenia during the entire trial period.

CONCLUSIONS

- **In a subgroup of patients who were treated according to treatment guidelines (i.e. with Grade 0 lymphopenia before the first course and Grade 0 or 1 lymphopenia before up to 3 subsequent annual courses of cladribine tablets [cumulative dose of up to 7 mg/kg]), at least 86% of patients recovered to Grade 0 or 1 lymphopenia by the end of each treatment year.**
- **In each year following additional courses of cladribine tablets, a similar proportion of patients recovered towards the normal range for lymphocyte counts.**
- **Grade 3 lymphopenia was uncommon, and no patients experienced Grade 4 lymphopenia at the end of any of the treatment years.**
- **Results of this study demonstrate the effectiveness of lymphocyte-based treatment criteria in minimizing the incidence of severe, sustained lymphopenia during four years' treatment with cladribine tablets.**

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DISCLOSURES

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. **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. **GG** has received speaker honoraria and consulting fees from Abbvie, 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. **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. **PS-S** has served on advisory boards for Biogen, Merck, Novartis, Teva, MedDay Pharmaceuticals, and GSK; on steering committees or independent data monitoring boards in trials sponsored by Merck, Teva, GSK, and Novartis; has received speaker honoraria from Biogen Idec, Merck, Teva, Sanofi-Aventis, Genzyme, and Novartis. His department has received research support from Biogen, Merck, Teva, Novartis, Roche, and Genzyme. **PV** has received honoraria or consulting fees from Biogen, Sanofi-Genzyme, Bayer, Novartis, Merck, Celgen, Roche, and Almirall; and research support from Biogen, Sanofi-Genzyme, Bayer, and Merck. **FD** is an employee of EMD Serono, Inc., a business of Merck KGaA, Darmstadt, Germany. **CH** is an employee of Merck KGaA, Darmstadt, Germany.

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