Innate Immune Cell Counts in Patients with Relapsing-Remitting Multiple Sclerosis (RRMS) Treated with Cladribine Tablets 3.5 mg/kg in CLARITY/CLARITY Extension

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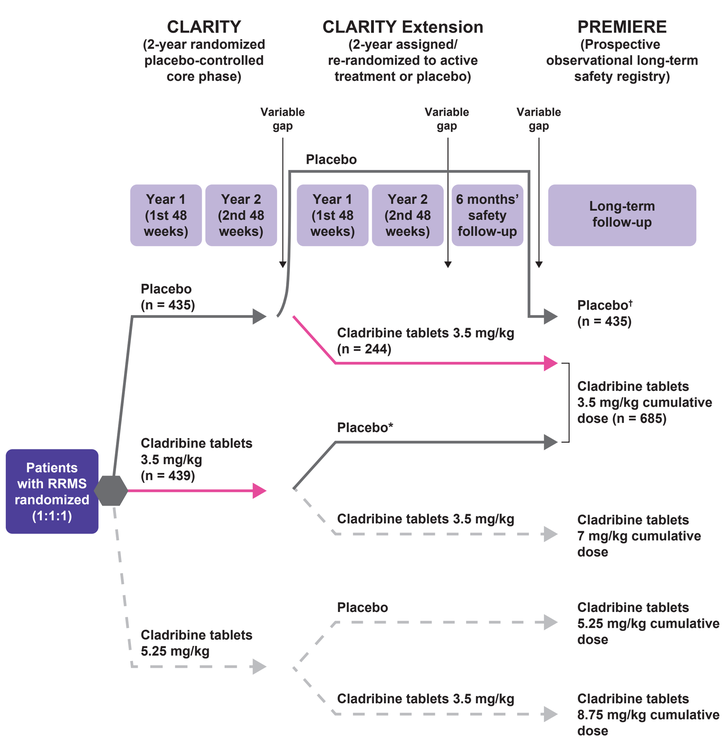
INTRODUCTION

- In the CLARITY study, cladribine tablets given annually for 2 years in short-duration courses significantly reduced relapse rates, disability progression, and magnetic resonance imaging measures of disease activity.[1]
- Patients who completed CLARITY were eligible to enter the CLARITY Extension study, in which they were re-randomized or assigned to cladribine tablets or placebo.[2]
- The most commonly reported adverse event in each study was lymphopenia, consistent with the mechanism of action for cladribine tablets.[1,2]
- Patients from CLARITY and CLARITY Extension were eligible for long-term observation of safety by entering the PREMIERE registry.

Figure 1. CLARITY Study Design



* Data from these patients were included in the cladribine tablets 3.5 mg/kg group for this analysis.
† Placebo patients in the PREMIERE registry included patients that entered directly from CLARITY, without being followed up in CLARITY Extension.
Solid lines indicate patient populations included in this analysis.

OBJECTIVE

- To evaluate the effect of cladribine tablets 3.5 mg/kg on innate immune cell counts.

METHODS

- Data from patients receiving a cumulative dose of cladribine tablets 3.5 mg/kg for years in CLARITY or CLARITY Extension, including time spent in the PREMIERE registry (n = 685) were pooled to provide long-term follow-up data, including information on neutrophil and monocyte counts.
- Data from patients randomized to placebo in CLARITY and followed up in CLARITY Extension and PREMIERE are also reported (n = 435).
- The CLARITY and CLARITY Extension study designs, and PREMIERE registry population are shown in **Figure 1**, to indicate the patient populations included in the analysis.
- Baseline was defined as the start of the active treatment period for the group randomized to cladribine tablets 3.5 mg/kg (i.e. after 2 years' placebo for patients initiating cladribine tablets 3.5 mg/kg in CLARITY Extension). In the placebo group, baseline was defined as the start of the CLARITY study.
- Patients who were randomized to placebo in CLARITY were assigned to cladribine tablets 3.5 mg/kg in CLARITY Extension. Patients who were not eligible for treatment with cladribine tablets in CLARITY Extension (as defined in the study protocol) were followed for safety only in the placebo group (**Figure 1**).
- One study year was defined as 48 weeks.

RESULTS

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

	Placebo (n = 435)	Cladribine Tablets 3.5 mg/kg (n = 685)
Time on study in weeks	168.67 (116.70)	205.13 (117.48)
Time on study Cumulative Interval at least 2 years (96 weeks), n (%)	337 (77.5)	597 (87.2)
Time on study Cumulative Interval at least 4 years (192 weeks), n (%)	91 (20.9)	286 (41.8)
Age in years*	38.7 (9.9)	38.2 (10.1)
Age ≤ 40 years, n (%)*	247 (56.8)	400 (58.4)
Age > 40 years, n (%)*	188 (43.2)	285 (41.6)
Female, n (%)*	286 (65.7)	462 (67.4)
Disease duration, years*	8.91 (7.39)	7.90 (6.91)
EDSS score	2.94 (1.31)	2.91 (1.37)
Prior treatment with DMD, n (%)	131 (30.1)	184 (26.9)

Data are mean (SD) unless otherwise stated.
* Baseline was defined as the start of the core studies for these parameters.
DMD, disease modifying drug; **EDSS**, Expanded Disability Status Scale.

Patients

- Patients exposed to cladribine tablets were more numerous and were followed over a longer period of time than patients receiving placebo. Patient demographics were similar between groups (**Table 1**).

Neutrophils

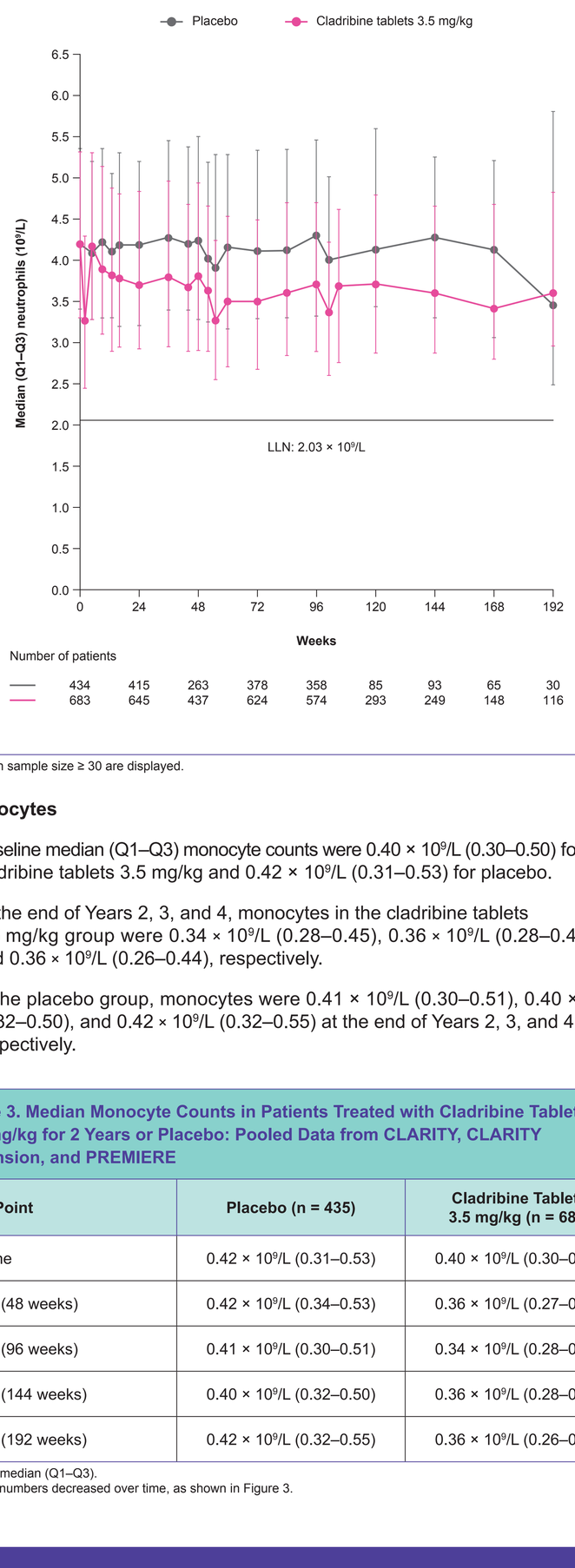
- Neutrophil counts over time are shown in **Figure 2**, and counts at baseline and the end of each year are shown in **Table 2**.
- At baseline (start of CLARITY or CLARITY Extension), median (Q1–Q3) neutrophil counts were 4.19 × 10^9/L (3.30–5.31) for cladribine tablets 3.5 mg/kg and 4.20 × 10^9/L (3.41–5.35) for placebo.
- Neutrophil counts remained within the normal range over the 2 treatment years and beyond, and this included the small decrease observed shortly after (2 to 5 weeks) each dose of cladribine tablets.
- At the end of Years 3 and 4 (144 and 192 weeks), median neutrophils in the cladribine tablets 3.5 mg/kg group (with no further treatment) plateaued at 3.60 × 10^9/L. In the placebo group, median neutrophils were 4.28 × 10^9/L and 3.46 × 10^9/L at the end of Years 3 and 4, respectively.
- Following treatment with cladribine tablets 3.5 mg/kg, neutrophil counts remained within the normal range (> 2.03 × 10^9/L) over the 2 treatment years and beyond:
  - At any single time point, Grade 3 or 4 neutropenia was reported in no more than 6 (< 2%) patients treated with cladribine tablets 3.5 mg/kg.

Table 2. Median Neutrophil Counts in Patients Treated with Cladribine Tablets 3.5 mg/kg for 2 Years or Placebo: Pooled Data from CLARITY, CLARITY Extension, and PREMIERE

Time Point	Placebo (n = 435)	Cladribine Tablets 3.5 mg/kg (n = 685)
Baseline	4.20 × 10^9/L (3.41–5.35)	4.19 × 10^9/L (3.30–5.31)
Year 1 (48 weeks)	4.24 × 10^9/L (3.28–5.50)	3.80 × 10^9/L (2.91–4.94)
Year 2 (96 weeks)	4.30 × 10^9/L (3.32–5.46)	3.71 × 10^9/L (2.90–4.70)
Year 3 (144 weeks)	4.28 × 10^9/L (3.30–5.25)	3.60 × 10^9/L (2.88–4.66)
Year 4 (192 weeks)	3.46 × 10^9/L (2.49–5.80)	3.60 × 10^9/L (2.96–4.82)

Data are median (Q1–Q3).
* Patient numbers decreased over time as shown in Figure 2.

Figure 2. Median Neutrophil Counts Over Time in Patients Treated with Cladribine Tablets 3.5 mg/kg for 2 Years or Placebo: Pooled Data from CLARITY, CLARITY Extension, and PREMIERE



Visits with sample size ≥ 30 are displayed.

Monocytes

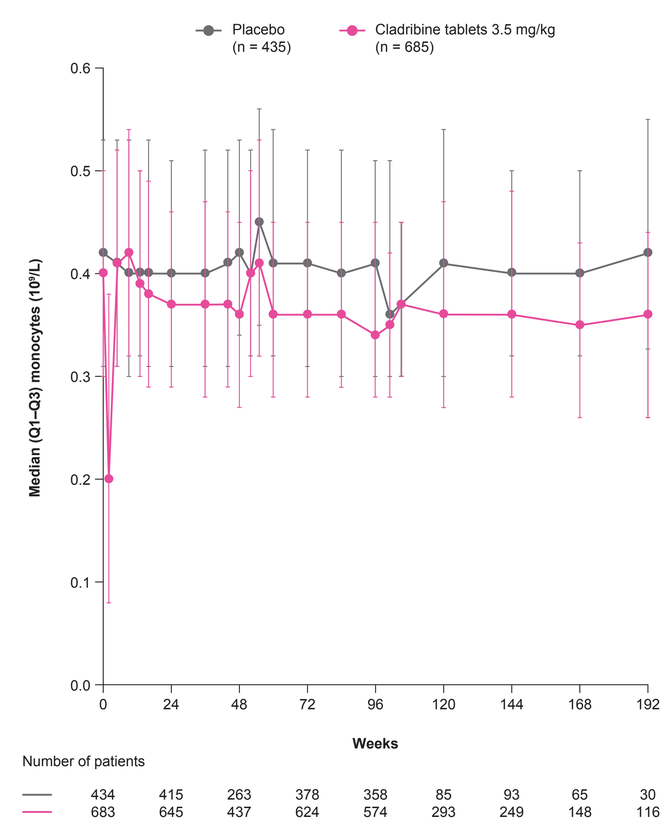
- Baseline median (Q1–Q3) monocyte counts were 0.40 × 10^9/L (0.30–0.50) for cladribine tablets 3.5 mg/kg and 0.42 × 10^9/L (0.31–0.53) for placebo.
- At the end of Years 2, 3, and 4, monocytes in the cladribine tablets 3.5 mg/kg group were 0.34 × 10^9/L (0.28–0.45), 0.36 × 10^9/L (0.28–0.48), and 0.36 × 10^9/L (0.26–0.44), respectively.
- In the placebo group, monocytes were 0.41 × 10^9/L (0.30–0.51), 0.40 × 10^9/L (0.32–0.50), and 0.42 × 10^9/L (0.32–0.55) at the end of Years 2, 3, and 4, respectively.

Table 3. Median Monocyte Counts in Patients Treated with Cladribine Tablets 3.5 mg/kg for 2 Years or Placebo: Pooled Data from CLARITY, CLARITY Extension, and PREMIERE

Time Point	Placebo (n = 435)	Cladribine Tablets 3.5 mg/kg (n = 685)
Baseline	0.42 × 10^9/L (0.31–0.53)	0.40 × 10^9/L (0.30–0.50)
Year 1 (48 weeks)	0.42 × 10^9/L (0.34–0.53)	0.36 × 10^9/L (0.27–0.45)
Year 2 (96 weeks)	0.41 × 10^9/L (0.30–0.51)	0.34 × 10^9/L (0.28–0.45)
Year 3 (144 weeks)	0.40 × 10^9/L (0.32–0.50)	0.36 × 10^9/L (0.28–0.48)
Year 4 (192 weeks)	0.42 × 10^9/L (0.32–0.55)	0.36 × 10^9/L (0.26–0.44)

Data are median (Q1–Q3).
* Patient numbers decreased over time, as shown in Figure 3.

Figure 3. Median Monocyte Counts Over Time in Patients Treated with Cladribine Tablets 3.5 mg/kg for 2 Years or Placebo: Pooled Data from CLARITY, CLARITY Extension, and PREMIERE



Visits with sample size ≥ 30 are displayed.

CONCLUSION

- **These data, together with the previously-reported data on absolute lymphocyte counts support the concept that cladribine tablets selectively reduce adaptive immune cell counts, and that the impact on the innate immune system is relatively minor.**

REFERENCES

1. Giovannoni G, et al. *N Engl J Med.* 2010;362:416-426.
2. Giovannoni G et al. *Mult Scler J.* 2017; in press.

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DISCLOSURES

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. **FD** is an employee of EMD Serono, Inc., a business of Merck KGaA, Darmstadt, Germany. **CH** is an employee of Merck KGaA, Darmstadt, Germany. **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.

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