Effects of Cladribine Tablets on B and T Lymphocytes and Natural Killer Cells in Patients with Early and Relapsing MS

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INTRODUCTION

- The efficacy of cladribine tablets 3.5 mg/kg (cumulative dose given in short courses annually for 2 years) has been demonstrated in patients with early multiple sclerosis in the ORACLE-MS study,[1] and in patients with relapsing-remitting multiple sclerosis in the CLARITY study,[2] maintained in the CLARITY Extension study.[3]
- The most common adverse event in CLARITY and CLARITY Extension was lymphopenia, consistent with the mechanism of action of cladribine tablets.[2,3]

OBJECTIVES

- To evaluate the effect of cladribine tablets on B and T lymphocyte and natural killer (NK) cell profiles after the first administration of cladribine tablets in the ORACLE-MS,[1] CLARITY[2] and CLARITY Extension[3] studies.

METHODS

- A longitudinal (48 weeks) evaluation of peripheral blood lymphocyte subtypes was conducted for patients receiving the first course of cladribine tablets either as part of the initial 3.5 mg/kg active treatment groups (ORACLE-MS and CLARITY) or the placebo-switched-to-active-treatment group (CLARITY Extension).
  - Patients from CLARITY Extension included in this analysis had received placebo in CLARITY and switched to cladribine tablets 3.5 mg/kg in the Extension phase. For these patients, lymphocyte surface markers (LSM) measurements that were available in CLARITY are included in the CLARITY Placebo group.
- Lymphocyte subset analyses were performed using flow cytometry to detect lymphocytes expressing CD3+, CD4+, CD8+, CD19+ or CD16+/CD56+ LSM.
- Blood samples for the LSM analysis were collected from a subset of patients in each study, and immunophenotypes are reported at baseline and at Weeks 5, 13, 24 and 48.
- Changes in absolute cell numbers and changes in the relative proportion of the lymphocyte subtypes were evaluated.
- Patients with at least one LSM assessment were included in this analysis.
- Patients who received rescue medication in CLARITY/CLARITY Extension, or interferon beta-1a in ORACLE-MS, had their LSM data censored from the time of starting rescue medication/interferon beta-1a.

RESULTS

Patients

- Baseline demographics and clinical characteristics of patients with LSM data from CLARITY, CLARITY Extension and ORACLE-MS are shown in **Table 1**.
- The baseline distributions of absolute lymphocyte counts (ALC) were similar across the 3 studies.

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

	CLARITY (N = 190)	CLARITY Extension (N = 136)	ORACLE-MS (N = 88)
Age, years	38.6 (10.4)	39.7 (9.2)	31.7 (8.7)
Female, n (%)	123 (64.7)	84 (61.8)	63 (71.6)
Time on study to end of Year 1, n (%)			
0–12 weeks	1 (0.5)	2 (1.5)	3 (3.4)
>12–24 weeks	1 (0.5)	0	6 (6.8)
>24–36 weeks	4 (2.1)	1 (0.7)	6 (6.8)
>36–48 weeks	169 (88.9)	93 (68.4)	23 (26.1)
>48 weeks	15 (7.9)	40 (29.4)	50 (56.8)
Patients in each treatment arm, n (%)			
CT 3.5 mg/kg	97 (51)	136 (100)	41 (47)
Placebo	93 (49)	-	47 (53)
Baseline ALC, 10^9/L	1.79 (0.57)	1.96 (0.64)	1.88 (0.57)

Data are mean (SD) unless stated otherwise.
ALC, Absolute lymphocyte count; **CT**, Cladribine tablets; **LSM**, lymphocyte surface marker; **n**, number of patients; **SD**, standard deviation.

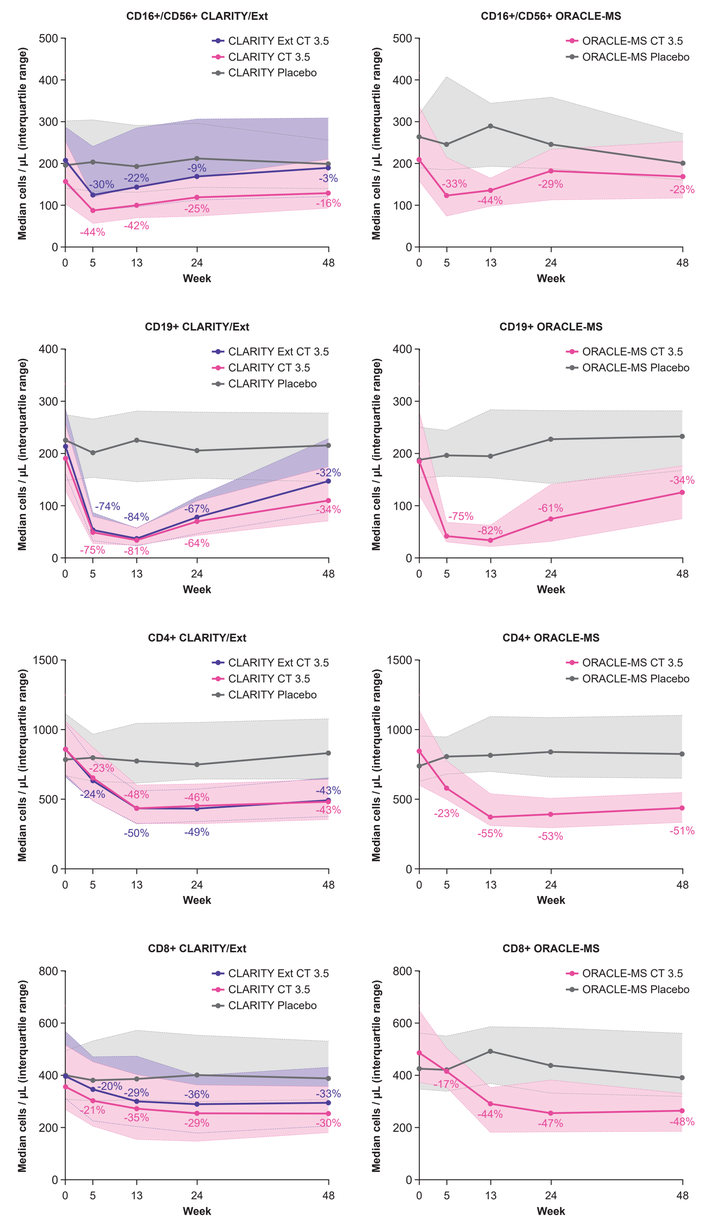
Lymphocyte Subtype Profiles

- Profiles of CD16+/CD56+ NK lymphocytes, CD19+ B lymphocytes, and CD4+ and CD8+ T lymphocytes were generally consistent across studies (**Figure 1**).
- CD16+/CD56+ NK cells were transiently reduced with cladribine tablets, with a prominent reduction at Week 5 followed by reconstitution towards baseline from Week 13 to 48. The interquartile ranges for cladribine tablets and placebo patients overlapped for the majority of the observation period.
- A large reduction in cell numbers occurred in the CD19+ B cell compartment (reductions from baseline of approximately 75% at Week 5 in each study).
  - Nadir was achieved at Week 13, followed by reconstitution towards baseline from Week 24 to 48.
- CD4+ and CD8+ T cells were also markedly reduced in numbers, but to a lesser degree than CD16+/CD56+ NK cells and CD19+ B cells.
- Reductions of both CD4+ and CD8+ T cells were discontinuous, but had not fully returned to baseline at Week 48 in patients treated with cladribine tablets in each study.

Lymphocyte Subtype Proportions of ALC

- The changes from baseline in CD16+/56+ NK cells and CD19+ B cells as proportions of ALC are shown in **Figure 2**.
- CD16+/56+ NK cell proportions increased by 6% to 19% at ALC nadir and by 28% to 38% at Week 48 compared with baseline lymphocyte subtype proportions.

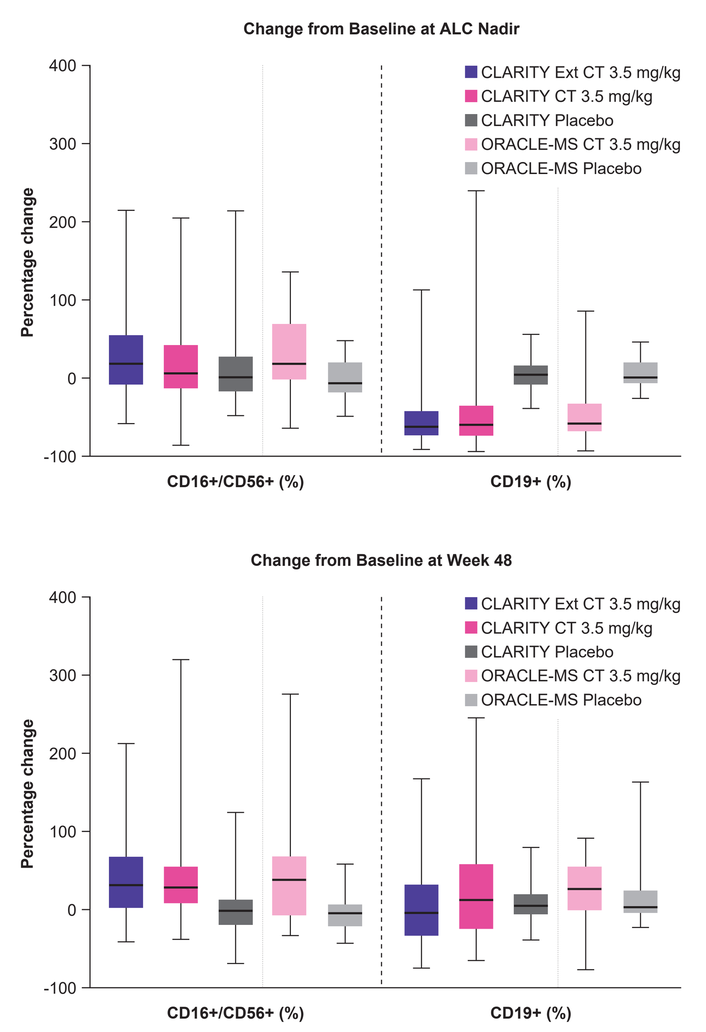
Figure 1. Median Lymphocyte Subtype Counts



Plots show median absolute cell counts (Q1–Q3); percentages are median % change from baseline in CT-treated patients. N.B. Timings of the lowest median absolute values do not necessarily correspond to the timings of the greatest median % reductions from baseline.
CT, Cladribine tablets; **Ext**, Extension.

- Large reductions (-58% to -62%) in the relative proportion of CD19+ B cells at ALC nadir across the 3 studies confirmed the effect of cladribine tablets on CD19+ B cells.
- At Week 48, the median proportion of CD19+ B cells was between -4% and +26% of the baseline lymphocyte subtype proportion across the 3 studies.

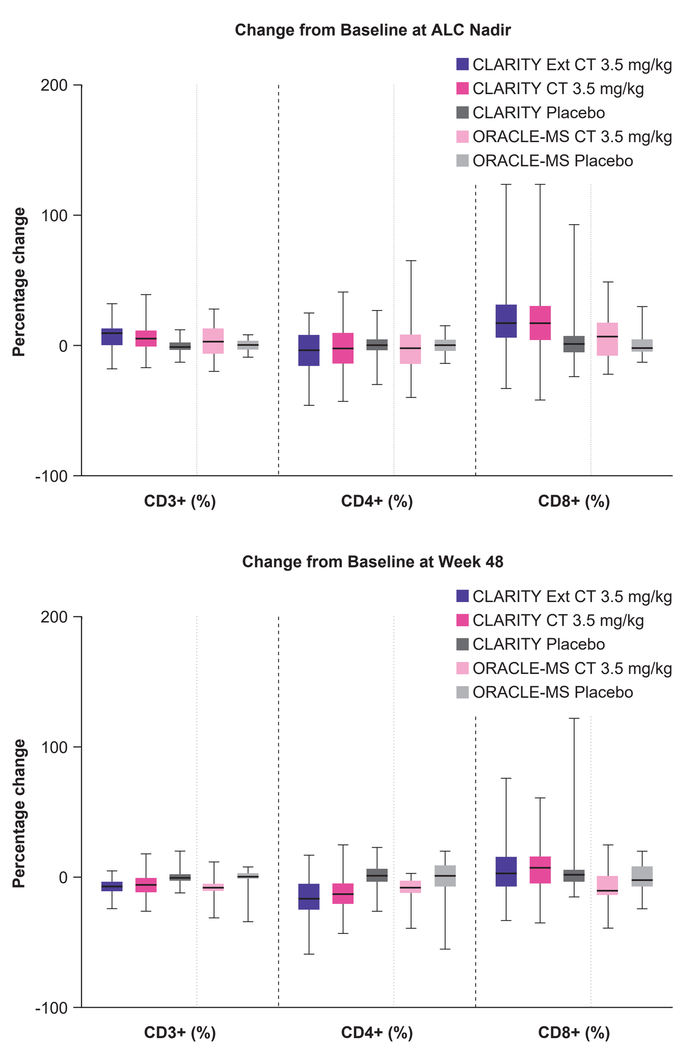
Figure 2. Percentage Change in Proportions from Baseline of LSM Subtypes: NK Cells and B Cells



Lines within boxes represent median values, boxes represent Q1–Q3 values, whiskers represent minimum and maximum values.
ALC, Absolute lymphocyte count; **CT**, Cladribine tablets; **Ext**, Extension: **LSM**, lymphocyte surface marker; **NK**, natural killer.

- The changes from baseline in CD3+, CD4+ and CD8+ T cells as proportions of ALC are shown in **Figure 3**.
- Lymphocyte subtype proportions of CD3+ cells were similar to baseline at ALC nadir and Week 48.
- Lymphocyte subtype proportions of CD4+ T cells at ALC nadir decreased by -2% to -4%, and by -8% to -16% at Week 48, compared with baseline lymphocyte subtype proportions in patients treated with cladribine tablets in CLARITY, CLARITY Extension or ORACLE-MS.
- Lymphocyte subtype proportions of CD8+ T cells at ALC nadir increased by 7% to 17%, and were between -10% and 7% at Week 48 compared with baseline lymphocyte subtype proportions.

Figure 3. Percentage Change in Proportions from Baseline of LSM Subtypes: T Cells



Lines within boxes represent median values, boxes represent Q1–Q3 values, whiskers represent minimum and maximum values.
ALC, Absolute lymphocyte count; **CT**, Cladribine tablets; **Ext**, Extension; **LSM**, lymphocyte surface marker.

CONCLUSIONS

- **In patients treated with cladribine tablets, early decreases in NK cells were observed followed by rapid recovery; there was a large degree of overlap in interquartile ranges between cladribine tablets and placebo.**
- **Peripheral B cell reductions were discontinuous, with an early reduction of counts followed by a rapid reconstitution towards baseline. This effect was consistent across the 3 studies.**
- **There was a moderate and discontinuous reduction in T cell counts, which was more pronounced in CD4+ than CD8+ lymphocytes.**
- **Changes in B cells as a proportion of ALC at ALC nadir were normalised by Week 48.**
- **At Week 48, there was a small reduction from baseline in CD4+ T cells as a proportion of the ALC.**

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DISCLOSURES

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