Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Giovannoni G, Comi G, Cook S, et al. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. N Engl J Med 2010;362:416-26. DOI: 10.1056/NEJMoa0902533.

APPENDIX: SUPPLEMENTAL INFORMATION

METHODS

ADDITIONAL STUDY DETAILS

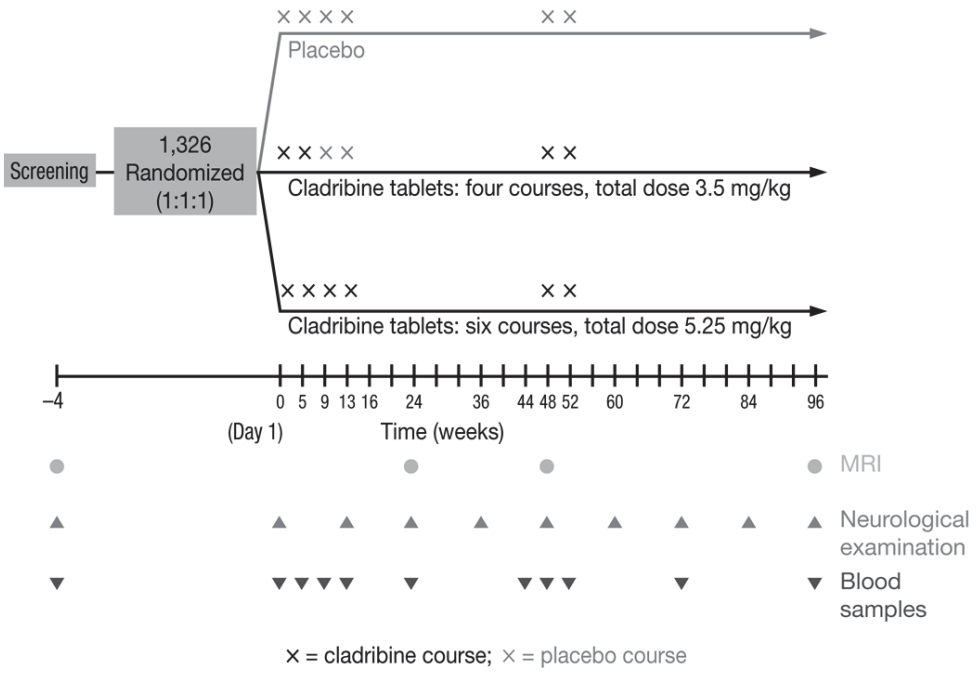
CLARITY – safety and efficacy of oral cladribine in subjects with relapsing-remitting multiple sclerosis, ClinicalTrials.gov identifier: NCT00213135, EudraCT number: 2004-005148-28

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and the International Conference on Harmonization Tripartite Guidelines for Good Clinical Practice.

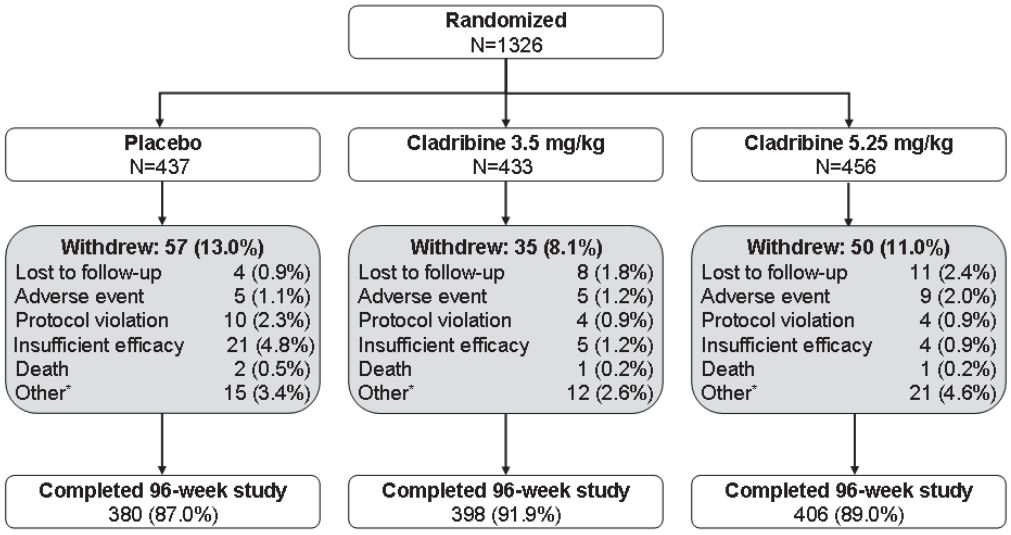
ASSESSMENT SCHEDULE

Clinical laboratory tests, including chemistry, hematology and urinalysis, were performed by a central laboratory at pre-study evaluation and at Study Day 1 and Weeks 5, 9, 13, 16, 24, 36, 44, 48, 52, 60, 72, 84 and 96 (see Supplemental Figure 1). Hematology analyses were also conducted at Weeks 2, 55, 66 and 78.

Supplemental Figure 1. Study design and timing of assessments



Supplemental Figure 2. Patient Enrollment and Disposition.



Withdrawal data shown are study discontinuations.

*Other reasons for discontinuation in the placebo and cladribine 3.5 and 5.25 mg/kg groups comprise consent withdrawal for administrative, convenience and personal reasons.

Note: Two deaths occurred after patients withdrew from study, one in each cladribine group.

PROTOCOL FOR THE MANAGEMENT OF HEMATOLOGICAL EVENTS

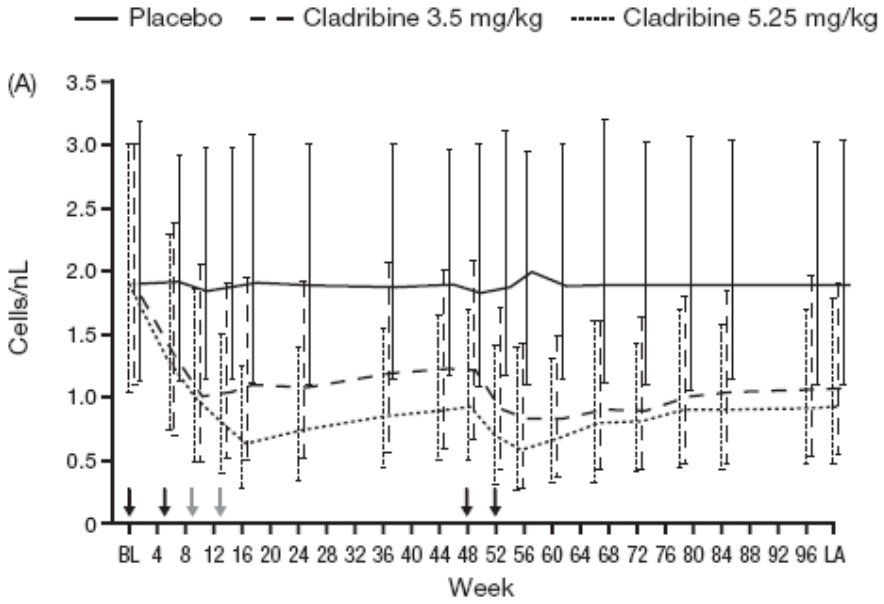
For severe events (Grade 3) attributable to the study drug, treatment could be interrupted at the discretion of the investigator until resolution to a mild/moderate event (Grade 0 or 1). This could be repeated if the Grade 3 event reoccurred, but treatment discontinuation was required for a third recurrence of Grade 3 event, its persistence after a 4-week treatment interruption, or the occurrence of Grade 4 toxicity. For hematological parameters, the threshold levels for discontinuation (Grade 4 toxicity values) were defined as hemoglobin levels of <4.0 mmol/L (65 g/L); leukocyte counts (total white blood cells) of <1 $x10^9$ /L; platelet counts of <25 $x10^9$ /L; and lymphocyte counts of <0.2 $x10^9$ /L.

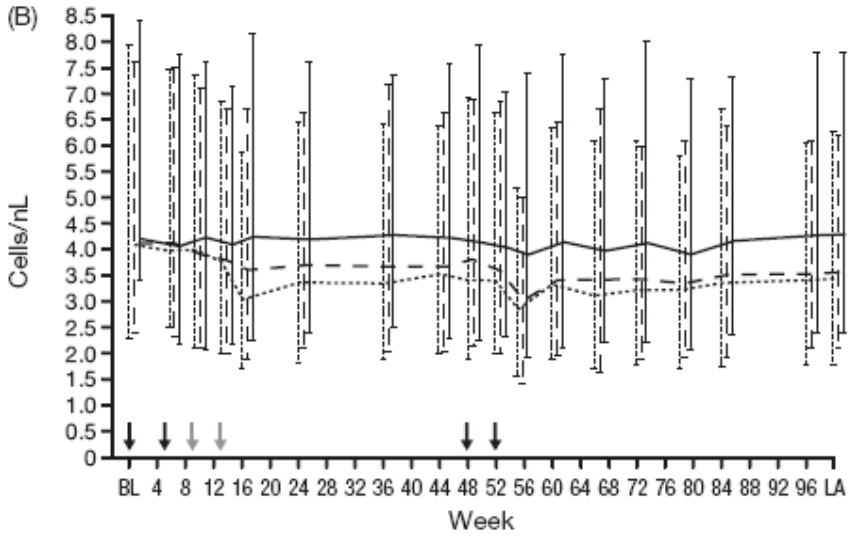
RESULTS

EFFECTS ON PERIPHERAL LYMPHOCYTES AND NEUTROPHILS

Treatment with cladribine tablets resulted in a rapid reduction in median lymphocyte counts reaching nadir values at Week 9 (change from baseline –45.8%) for the cladribine tablets 3.5 mg/kg treatment group, and at Week 16 (change from baseline –64.0%) for the cladribine tablets 5.25 mg/kg treatment group, i.e. at 3–4 weeks after completion of the active treatment courses (Supplemental Figure 3). A gradual, only modest increase in median lymphocyte counts ensued and at Week 48, prior to initiation of re-treatment, median lymphocyte counts were –35.6% and –49.6% from baseline for the cladribine tablets 3.5 mg/kg and 5.25 mg/kg treatment groups, respectively. Re-treatment in the second 48-week treatment period with two additional cladribine tablets treatment courses resulted in an additional, but lesser magnitude reduction in median lymphocyte counts that reached nadir 3–8 weeks after last treatment (Week 60 for the 3.5 mg/kg group, and Week 55 for the 5.25 mg/kg group) followed again by gradual return to levels seen prior to re-treatment. Reductions in median lymphocytes persisted to study end (–43.5% and –48.3% from baseline at Week 96, and –43.3% and –48.3% at last assessment for the cladribine tablets 3.5 mg/kg and 5.25 mg/kg treatment groups, respectively). The overall effect on reduction in median neutrophil counts was much less pronounced by comparison, with median neutrophil counts –15.4% and –18.0% from baseline at Week 96 and –15.4% and –17.5% at last assessment for the cladribine tablets 3.5 mg/kg and 5.25 mg/kg treatment groups, respectively (Supplemental Figure 3).

Supplemental Figure 3. Median Cell Counts by Treatment Group Over Time for (A) Lymphocytes and (B) Neutrophils





Placebo N=434; cladribine 3.5 mg/kg N=428; cladribine 5.25 mg/kg N=451
BL = baseline; LA = last assessment

Estimates for the median used the Hodges-Lehmann estimator based on the Sign statistic.

Error bars indicate the 5-95 percentile range for cell counts at each time point.

Arrows indicate start of each short-course of treatment: black arrows indicate cladribine tablets courses; grey arrows indicate placebo course for the 3.5 mg/kg group and cladribine tablets for the 5.25 mg/kg group

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