Cladribine and progressive MS

Clinical and MRI outcomes of a multicenter controlled trial

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Article abstract—*Objective:* To evaluate the safety and efficacy of two doses of cladribine in patients with progressive MS. *Background:* Treatment of progressive MS patients with cladribine in a previous single-center, placebo-controlled clinical trial was associated with disease stabilization. *Methods:* In the current study, 159 patients with a median baseline Kurtzke's Expanded Disability Status Scale (EDSS) score of 6.0 were randomly assigned to receive placebo or cladribine 0.07 mg/kg/day for 5 consecutive days every 4 weeks for either two or six cycles (total dose, 0.7 mg/kg or 2.1 mg/kg, respectively), followed by placebo, for a total of eight cycles. Thirty percent had primary progressive MS (PPMS) and 70% had secondary progressive MS (SPMS). EDSS and Scripps Neurologic Rating Scale (SNRS) scores were assessed bimonthly and MRI was performed every 6 months. The primary outcome measure was disability (mean change in EDSS). *Results:* Mean changes in disability did not differ among the groups at the end of the 12-month double-blind phase. Both cladribine treatments were superior to placebo for the proportion of patients having gadolinium-enhanced T1 lesions and for the mean volume and number of such lesions ($p \leq 0.003$). Differences were statistically significant at the 6-month evaluation time, with ≥90% reduction in volume and number of enhanced T1 lesions, which was maintained through final evaluation. This effect segregated largely with the SPMS group. The T2 burden of disease showed a modest improvement in cladribine-treated patients and worsened in placebo-treated patients. Most adverse events were mild or moderate in severity and not treatment limiting. *Conclusion:* No significant treatment effects were found for cladribine in terms of changes in EDSS or SNRS scores. Both doses of cladribine produced and sustained significant reductions in the presence, number, and volume of gadolinium-enhanced T1 brain lesions on MRI, and cladribine 2.1 mg/kg reduced the accumulation of T2 lesion load. Cladribine at doses up to 2.1 mg/kg was generally safe and well tolerated. **Key words:** Cladribine—MRI—Progressive MS—Suppression of disease activity.

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With the exception of trauma, MS—a demyelinating disease of the CNS with an estimated prevalence of 250,000 to 350,000 in the United States and 1.1 million worldwide—is the most common cause of neurologic disability in young adults.[1] About two thirds of patients develop a relapsing-remitting pattern (RRMS), and the majority of these will experience a progressive deterioration, or secondary progressive MS (SPMS); about 15% of patients appear to have a progressive course from onset, or primary progressive MS (PPMS).[2] The mandate for prevention of disease progression is compelling. The natural history of progressive MS has been little altered, at least in the short term, by currently available agents. β-Interferons have been reported to be effective in the treatment of RRMS,[3-13] and recently, interferon β-1b has been reported to delay the time to confirmed progression in patients with SPMS by 9 to 12 months.[14]

MRI has allowed direct visualization of the number, location, and volume of acute and chronic lesions associated with underlying disease pathology, and some correlations between MRI and clinical parameters have been demonstrated.[15] In patients with RRMS and SPMS, there is a correlation between the frequency and extent of lesion enhancement and short-term disease activity.[16-19] In clinical trials, the presence of contrast-enhanced T1 lesions at baseline has been shown to predict both clinical and MRI activity in the following 6 months,[19] and, in patients with clinically isolated syndromes suggestive of MS, T2 lesion load at presentation is strongly correlated with disability after 5 years.[20,21] A recent meta-analysis of data from nine studies in 307 patients with RRMS and SPMS, however, found that although enhancement predicts the occurrence of relapses it is not a strong predictor of subsequent accumulation of disability over a 2-year period of observation.[22] Phase III clinical trials evaluating new therapies for MS now almost always include MRI evaluations along with traditional clinical assessments.[15,23]

Cladribine (2-chlorodeoxyadenosine; 2-CdA) is a purine nucleoside analogue resistant to the action of

*See Appendix 1 on page 1154 for a listing of members of the Cladribine Study Group and the Cladribine MRI Study Group.

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adenosine deaminase, which results in preferential lymphocytotoxicity. In cells with a high ratio of deoxycytidine kinase to deoxynucleotidase (e.g., lymphocytes and monocytes), cladribine is phosphorylated into the active triphosphate deoxynucleotide, 2-CdATP, which accumulates, causing a disruption of cellular metabolism, DNA damage, and subsequent cell death.[24] Its long-lasting lymphocytotoxic activity suggests that cladribine could be useful in modulating autoimmune processes involving lymphocyte abnormalities such as MS. Sipe and colleagues have reported the outcome of a placebo-controlled clinical trial of cladribine in patients with progressive MS.[25,26] Treatment with a total dose of 2.8 mg/kg cladribine was associated with significant stabilization of the disease in patients with SPMS. Compared with a progression rate of 50% of the patients treated with placebo, 95% of cladribine-treated patients were stable at 1 year. These clinical observations were supported by favorable effects in the MRI brain scans, i.e., nearly complete elimination of enhanced T1 lesions and stabilization of T2 lesion volume at final evaluation. Encouraged by this single-center study, a multicenter, double-blind, placebo-controlled trial was conducted to evaluate the safety and efficacy of two doses of cladribine in patients with progressive MS.

Methods. *Study population.* A total of 159 patients with progressive MS were enrolled at six clinical centers in the United States and Canada. Inclusion criteria for entry into the trial were clinically definite or laboratory-supported MS according to the Schumacher criteria[27] or Poser criteria[28] and defined as chronic progressive by the slow progression of signs and symptoms over the preceding 12 months; a baseline Expanded Disability Status Scale (EDSS)[29] score between 3.0 and 6.5; age 21 to 60 years; serum creatinine levels <1.5 mg/dL and creatinine clearance $\geq$ 80% of age-adjusted normal value; aspartate and alanine transaminase (AST and ALT) and alkaline phosphatase levels less than twice the normal upper limit; neutrophil count $>1600/\mu L$ and platelet count $>130{,}000/\mu L$; and clinically normal ECG and chest x-ray. Patients were excluded from the trial if there was significant history of medical disease within the preceding 2 years that would impair participation in the trial; use of corticosteroids or other immunosuppressants such as cyclophosphamide, azathioprine, cyclosporine, or β-interferon within the preceding 3 months; total lymphoid irradiation; persistent leukopenia or thrombocytopenia after treatment with immunosuppressive agents; history of alcohol or drug abuse within the preceding year or of attempted suicide; malignancy or history of malignancy within the preceding 5 years; pregnancy or nursing; positive test result for HIV; use of an experimental drug or device within the preceding 60 days; or prior participation in a trial with cladribine. The protocol was approved by the respective institutional review boards, and patients signed informed consent forms.

Study design. This multicenter trial was a randomized, double-blind, parallel-group, placebo-controlled study of cladribine and placebo administered by subcutaneous (SC) injection in patients with progressive MS, to evaluate the dose-response relationship, and to obtain information concerning the duration of any effects. The study included a 4-week screening phase, a 1-year double-blind phase, and a 6-year long-term extension. Patients were assigned to one of three parallel treatment groups (cladribine, 2.1 mg/kg; cladribine, 0.7 mg/kg; or placebo) according to a computer-generated randomization schedule stratified by baseline disease severity and site. Sample size computation was based on an assumed SD of 1.7 for change from the baseline EDSS score. The planned sample size of 50 patients per treatment group would have a statistical power of 80% based on a two-sided alpha of 0.05 to detect a difference of 1.0 in change from the baseline EDSS score between the cladribine, 2.1 mg/kg, and placebo groups.

The trial was initiated in December 1994. During the 1-year double-blind phase, patients were evaluated monthly for vital signs, adverse events, and a complete blood count (CBC) that was obtained just before the monthly visit. Neurologic status was evaluated bimonthly by assessment of EDSS and Scripps Neurologic Rating Scale (SNRS) scores by the blinded clinical investigators, who underwent standardized training. Brain MRI scans were obtained at baseline and months 6 and 12, as were total lymphocyte count and lymphocyte subset counts ($CD3^+$, $CD4^+$, $CD8^+$, $CD19^+$, $CD16^+$ plus $CD56^+$, and $CD4^+/CD8^+$ ratio). Physical examinations were performed at baseline and months 4, 8, and 12; a chemistry panel and urinalysis were performed periodically, and an ECG was obtained at the end of the treatment phase. During the first year of the post-double-blind follow-up phase, EDSS scores, CBC, and lymphocyte counts were assessed quarterly; MRI scans were obtained at months 18 and 24.

In addition to the treating physician, an examining physician was designated at each site to assess the patient's neurologic function using EDSS and SNRS scoring. All study investigators and patients were blinded to treatment assignment; adverse events and unblinded hematology results were routinely reviewed by an independent safety monitoring board. After all patients at a study site completed the 12-month double-blind phase, the blind was broken, and patients who fulfilled the hematologic dosing criteria were permitted to receive open-label cladribine treatment during the long-term extension phase of the study, provided at least 12 months had elapsed since the last dose of cladribine and there was evidence of disease progression. Patients treated with open-label cladribine were evaluated monthly for 12 months following initiation of the drug, and then quarterly.

Study medications and dosage. Patients who met the protocol-specified entry criteria were randomized in approximately equal numbers to receive eight monthly courses of therapy. Patients received six courses of cladribine 0.07 mg/kg/day SC for 5 consecutive days (total dose, 2.1 mg/kg), followed by two courses of placebo or two courses of cladribine 0.07 mg/kg/day SC for 5 consecutive days (total dose, 0.7 mg/kg), followed by six courses of placebo or eight courses of placebo SC for 5 consecutive days. To receive a subsequent course of blinded study drug, patients were required to meet the hematologic criteria, which were based on the results of a CBC obtained 2 to

dix 2. For a patient who did not meet these criteria, placebo was substituted for the active drug for that dosing period. If the hematologic criteria for dosing were met at the next evaluation, the patient received active drug the following month, up to the eighth month. All CBC data were reviewed by an independent third party. The treating physician remained blinded but was provided with any abnormal CBC results required for proper medical management.

Concomitant therapy. Methylprednisolone, 1 g/day for up to 5 days, was allowed only for treatment of severe exacerbations. In addition, patients were allowed to continue receiving symptomatic therapies to treat troublesome symptoms of MS (e.g., baclofen for spasticity or oxybutynin chloride for bladder dysfunction).

MRI evaluation. Dual-echo conventional spin-echo images were obtained using repetition times of 2500 msec and echo times of 30 (proton-density weighting) and 90 (T2 weighting) msec. T1-weighted images were obtained using repetition times of 600 msec and echo times of 20 msec. For both sequences, slices were axial with a matrix size of 256 × 256 mm and a field of view of 200 × 200 mm. Sections were 4 mm thick with a 1-mm interslice gap for the dual-echo scans and 3 mm thick and contiguous for the T1-weighted scans. The total imaging time was approximately 20 to 25 minutes. Special attention was given to careful repositioning of the patient, using laser guidance and external landmarks to help achieve reproducible slice positions. All scan data were blinded to treatment, date, and sequence of scan.

Lesion identification. *Postcontrast T1-weighted images.* A single experienced observer identified enhanced lesions following rules and criteria established in recently published guidelines.[30] Areas of enhancement were marked on transparent sheets superimposed over the scan hard copies, and then the total number of enhanced lesions per scan was counted. Corresponding dual-echo images were used to increase the confidence in lesion detection.

T2-weighted images. A single experienced observer identified hyperintense MS lesions and marked the corresponding areas on transparent sheets superimposed over the proton-density scan hard copies. Corresponding T2-weighted images were used to increase the confidence in lesion detection.

Lesion segmentation and measurement of lesion volume. Trained technicians measured the lesion volumes for the scans belonging to the same patient to avoid variabilities of interobserver measurement. A local thresholding technique was used for lesion segmentation on computer-displayed images, with the marked hard copies kept as a reference. This local thresholding technique for segmentation was provided by the Dispunc display software for MR images, developed by David Plummer (University College, London, UK). The observer first chooses a point on the lesion using a mouse-controlled cursor, and the algorithm starts contouring, following from the strongest edge point in the neighborhood of the user-selected point. This strongest edge point (i.e., the starting point) is found by searching over a 5 × 5 pixel square area with the manually selected point in its center. Once the algorithm has found the starting point, the program, searching in all directions and choosing the strongest one, finds the next contour starting point. The program then traces a contour from the most recent point, following the same principle described above; the contour is complete when it traces back to the starting point. The MS lesions detected are recorded in a file as regions of interest (ROIs) and superimposed on each image slice. The program automatically calculates the single ROI area. Manual outlining is required to modify part of the boundary of poorly defined lesions or (more rarely) to fully outline lesions not definable by contouring. The total lesion volume is then calculated, multiplying the total ROI area by the slice thickness. For the whole measurement process, the technicians followed recently published guidelines.[31]

Statistical analyses. Efficacy and safety analyses were based on the population of patients who received at least one dose of study medication and had available data. For efficacy variables, all hypothesis tests were carried out two-sided, with a significance level of <0.05 considered to be statistically significant.

The designated primary efficacy parameter was mean change in EDSS score from baseline to the final evaluation. Secondary clinical outcome measures were mean change from baseline in SNRS score and time to progression of MS. Disease progression was defined as an increase in EDSS score of ≥ 1.0 for patients with a baseline disability of 3.0 to 5.0 and an increase in EDSS score of ≥ 0.5 for patients with a baseline disability of 5.5 to 6.5, which was confirmed at the next scheduled visit. EDSS and SNRS examinations were performed by the blinded examining physician every second month during the double-blind phase. Treatment differences for the change from baseline to the final evaluation for these variables were assessed using a Wilcoxon's rank sum test. Comparisons were made between the placebo and cladribine 2.1 mg/kg groups and the placebo and cladribine 0.7 mg/kg groups, respectively. Time to progression of MS was analyzed using survival analysis methods. Kaplan-Meier estimates for the probabilities of failure were computed for each group. Log-rank tests were used to compare the distributions between the placebo and cladribine 2.1 mg/kg groups and between the placebo and cladribine 0.7 mg/kg groups.

The evaluation of MRI efficacy is based on the proportion of patients with contrast-enhanced T1-weighted brain lesions at the final evaluation. Additional MRI efficacy assessments are based on the number and volume of enhanced T1-weighted lesions and volume of T2-weighted lesions. Comparisons between treatment groups (placebo versus cladribine 2.1 mg/kg, placebo versus cladribine 0.7 mg/kg) of the proportion of patients with enhanced T1 lesions at months 6 and 12 and the final evaluation were made using Fisher's exact test. Treatment differences in enhanced T1 lesion volume and number, T2 lesion volume, and change and percent change in T2 lesion volume from baseline to final evaluation were assessed using Wilcoxon's rank sum test.

Safety analyses included summaries of adverse events. For laboratory analytes, vital signs, and body weights, means and mean changes from baseline were computed at each monthly visit.

Results. *Demographic and baseline characteristics.* The 159 eligible patients were randomly assigned to receive placebo (n = 54), cladribine 0.7 mg/kg (n = 53), or

***Table 1** Demographic and baseline characteristics*

Characteristic	Placebo (n = 54)	Cladribine 0.7 mg/kg (n = 53)	Cladribine 2.1 mg/kg (n = 52)
Age, mean (y)	44.2	44.6	43.8
% Male/female	37/63	42/58	50/50
Pattern of disease			
% PPMS	26	36	29
% SPMS	74	64	71
Duration of disease (y)			
Mean	12.3	10.9	10.6
Median	11.7	10.0	8.8
EDSS score at entry			
Mean	5.6	5.6	5.6
Median	6.0	6.0	6.0
Category, % 3.0–5.0/5.5–6.5	31/69	30/70	25/75
SNRS score at entry			
Mean	60.9	60.7	62.3
Median	62.0	62.0	62.0

PPMS = primary progressive MS; SPMS = secondary progressive MS; EDSS = Expanded Disability Status Scale; SNRS = Scripps Neurological Rating Scale.

were similar with respect to age, gender, duration and pattern of disease, and baseline disability as defined by EDSS or SNRS scores (table 1). Overall, the median age was 44 years; 43% of patients were men and 57% were women. At baseline, 111 (70%) patients had SPMS and 48 (30%) patients had PPMS; 71% of patients had a baseline EDSS score of ≥5.5, indicating a population with substantial disability. Consistent with a population of more advanced disease and 30% of patients with PPMS, 63% had no enhanced lesions at baseline. Mean enhanced T1 lesion count was 1.3, and mean enhanced T1 lesion volume was 216.4 μL at baseline. Mean T2 lesion volume at baseline was 12.0 mL. Patients in the placebo group had a somewhat smaller mean enhanced T1 lesion volume than patients in the two cladribine groups (p = NS), and T1 lesion volumes at baseline had higher standard deviations among the cladribine patients than among the placebo patients.

Compliance. All 159 patients randomized to receive double-blind therapy received at least one dose of the study drug, and all are included in the efficacy analysis; 155 (97%) patients completed the double-blind phase. There were no withdrawals due to adverse events; 4 (3%) patients withdrew voluntarily from the study (subject choice) before completion of the double-blind phase (three from the low-dose cladribine group and one from the higher-dose group). The majority of patients received all eight scheduled courses of therapy (7/54 placebo-treated patients, 11/53 cladribine 0.7 mg/kg-treated patients, and 16/52 of 2.1 mg/kg-treated patients received a placebo substitution). The most common reasons for failure of the dosing criteria were fluctuations in hemoglobin levels and platelet counts, which occurred at a similar frequency in all groups.

Post-double-blind follow-up data are available for 148 of

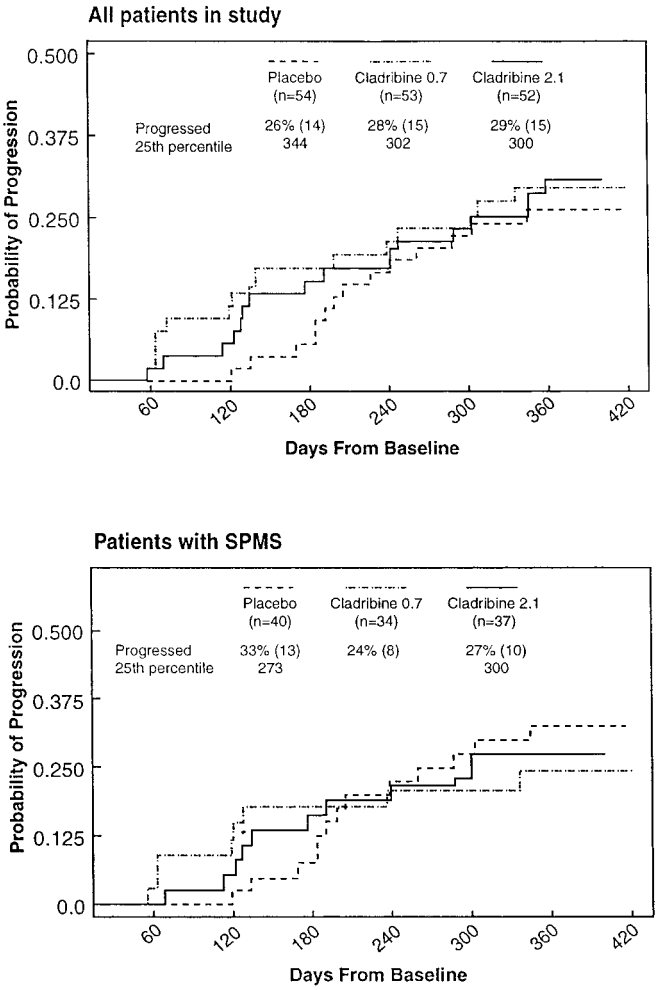

Figure 1. Probability of disease progression over time. SP = secondary progressive.

ongoing study. For the outcomes presented here, the mean duration of follow-up from the first dose was 29 months.

Clinical outcomes. During the 12-month double-blind phase, the mean changes in EDSS and SNRS scores from baseline to final evaluation were small in all three treatment arms (placebo, 0.7 mg/kg, and 2.1 mg/kg cladribine), and no differences among treatment groups were observed for placebo and cladribine. Examination of changes in EDSS scores according to pattern of disease showed that for patients with SPMS, EDSS scores increased modestly (0.3) over time in the placebo group but less in the active treatment groups (±0.0, p = NS); by comparison, very little change in EDSS score was experienced in any treatment arm by patients with PPMS. Similarly, although no significant differences among treatment groups were found in time to progression assessed by Kaplan-Meier estimate for all patients, there was a trend toward a more favorable clinical response to cladribine than to placebo in the SPMS subgroup (figure 1); 33% of patients in the placebo group met the criteria for disease progression by the end of the double-blind phase, compared with 24% to 27% of cladribine-treated patients with SPMS.

Exacerbations, steroid utilization, and hospitalizations did not differ among the three groups.

Follow-up EDSS scores obtained after the 12-month

Table 2 *Summary of MRI outcomes during double-blind phase of study: all patients*

	Placebo	Cladribine 0.7 mg/kg		Cladribine 2.1 mg/kg	
MRI parameter	n (%) or mean (SD)	n (%) or mean (SD)	*p* Value	n (%) or mean (SD)	*p* Value
Enhanced T1 lesions					
Proportion of patients with lesions (%)[a,b,d]					
Baseline	53 (38%)	52 (33%)		50 (36%)	
Month 6	51 (33%)	49 (12%)	0.0169	52 (2%)	0.001
Month 12	50 (32%)	48 (10%)	0.0131	48 (6%)	0.0017
Final evaluation	54 (31%)	51 (10%)	0.0080	52 (6%)	0.0009
Mean number of lesions (SD)[a,c,d]					
Baseline	1.17 (2.23)	1.64 (4.43)		1.10 (2.07)	
Month 6	0.78 (1.49)	0.17 (0.52)	0.008	0.12 (0.85)	<0.001
Month 12	0.57 (1.10)	0.13 (0.40)	0.007	0.09 (0.35)	0.001
Final evaluation	0.58 (1.12)	0.12 (0.39)	0.005	0.08 (0.34)	0.001
Mean volume of lesions in μL (SD)[a,c,d]					
Baseline	142.66 (302.15)	283.82 (803.10)		235.24 (777.94)	
Month 6	78.67 (168.07)	12.44 (44.35)	0.008	19.40 (137.18)	<0.001
Month 12	67.76 (119.65)	10.94 (39.99)	0.005	6.36 (26.63)	0.001
Final evaluation	78.11 (155.74)	10.28 (38.83)	0.003	5.98 (25.85)	0.001
T2 lesions					
Mean lesion volume (mL) (SD)[a,c,d]					
Baseline	12.90 (12.35)	13.03 (12.37)		9.91 (8.50)	
Month 6	13.45 (12.77)	13.15 (12.09)	0.872	9.78 (8.60)	0.155
Month 12	13.13 (13.11)	12.62 (11.52)	0.944	9.79 (8.80)	0.231
Final evaluation	13.31 (13.00)	12.65 (11.96)	0.868	9.71 (8.56)	0.180
Change from baseline to final evaluation[c,d,e]					
Mean (SD)	0.41 (1.72)	−0.39 (1.70)		−0.20 (1.13)	
Median	0.10	−0.01	0.055	−0.13	0.040
Percent change from baseline to final evaluation[c,d,e]					
Mean (SD)	1.81 (11.38)	−1.67 (14.98)		−3.93 (14.80)	
Median	1.53	0.03	0.144	−2.51	0.029

[a] Includes patients with both baseline and final evaluations.
[b] Fisher's exact test (two-sided significance).
[c] Based on Wilcoxon's (Mann-Whitney) rank sum test.
[d] The final evaluation is the last evaluation for each patient up to month 12 during year 1.
[e] Positive change indicates disease progression.

through month 24 for a sizable cohort of patients, although cohort sizes became smaller as some patients entered retreatment during the follow-up phase. Although mean EDSS scores increased over time in all treatment groups, scores for the follow-up period were also analyzed by pattern of disease. For patients with SPMS, mean changes in EDSS scores were somewhat more favorable with cladribine (0.2 and 0.3, respectively, for the 0.7-mg/kg and 2.1-mg/kg doses) compared with placebo (0.6) by 24 months. No difference was observed for patients with PPMS.

Magnetic resonance outcomes. Proportion of patients with enhanced T1 lesions. At baseline, approximately 35% of patients in each treatment group had enhanced T1 lesions (figure 2, table 2). Whereas the proportion of patients with enhanced T1 lesions remained nearly unchanged in the placebo group, the proportion of cladribine-treated patients with enhanced T1 lesions decreased significantly, to 10% in the 0.7 mg/kg group ($p = 0.0080$) and 6% in the 2.1 mg/kg group ($p = 0.0009$). By final evaluation, there was a 70% reduction in the proportion of patients with enhanced T1 lesions in the cladribine 0.7 mg/kg group and an 83% reduction in this proportion in the cladribine 2.1 mg/kg group, compared with a reduction of 18% in the placebo group. The difference between the cladribine and placebo groups in the proportion of patients with enhanced T1 lesions was statistically significant at month 6 (see figure 2, table 2). It remained significant through month 18 for the 0.7 mg/kg dose and through month 24 for the 2.1 mg/kg dose (table 3).

Subgroup analysis of the proportion of patients with

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