

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

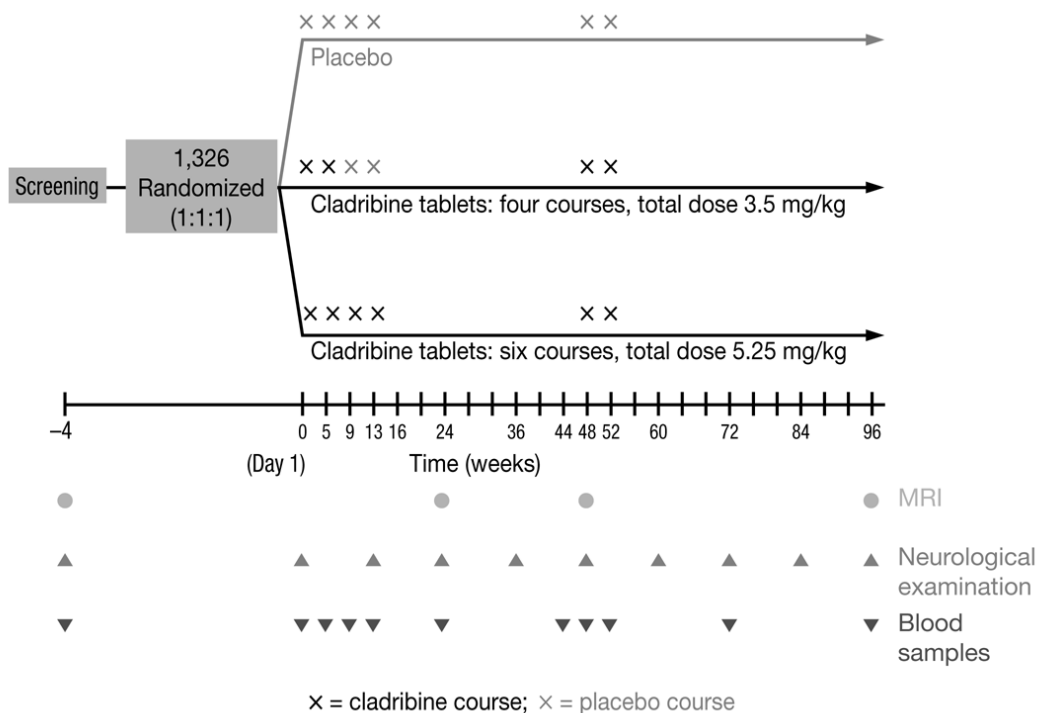
CLARITY – safety and efficacy of oral cladribine in subjects with relapsing-remitting multiple sclerosis, ClinicalTrials.gov identifier: NCT00213135, EudraCT number: 2004-005148-28

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.

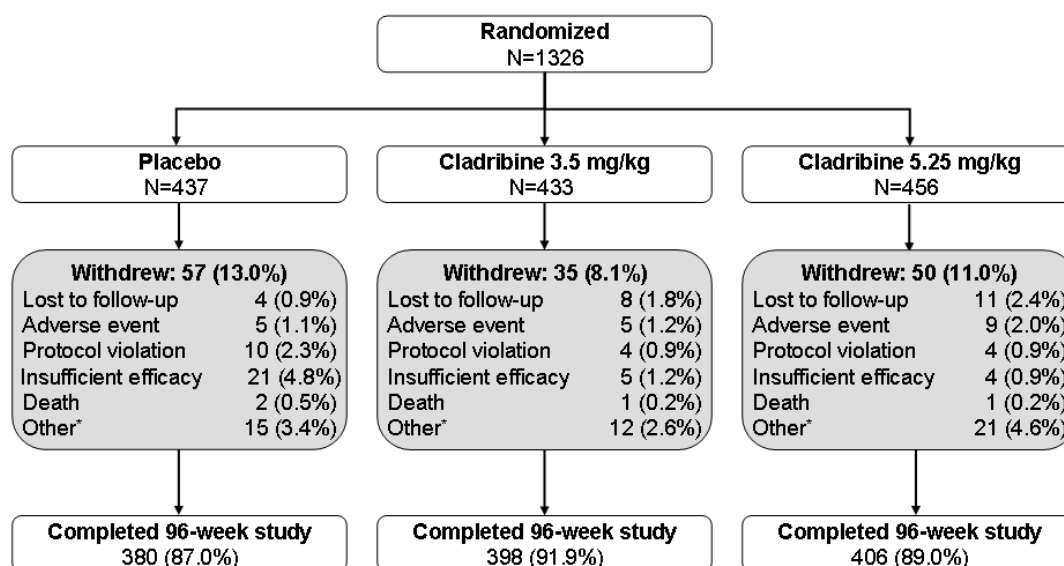
ASSESSMENT SCHEDULE

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

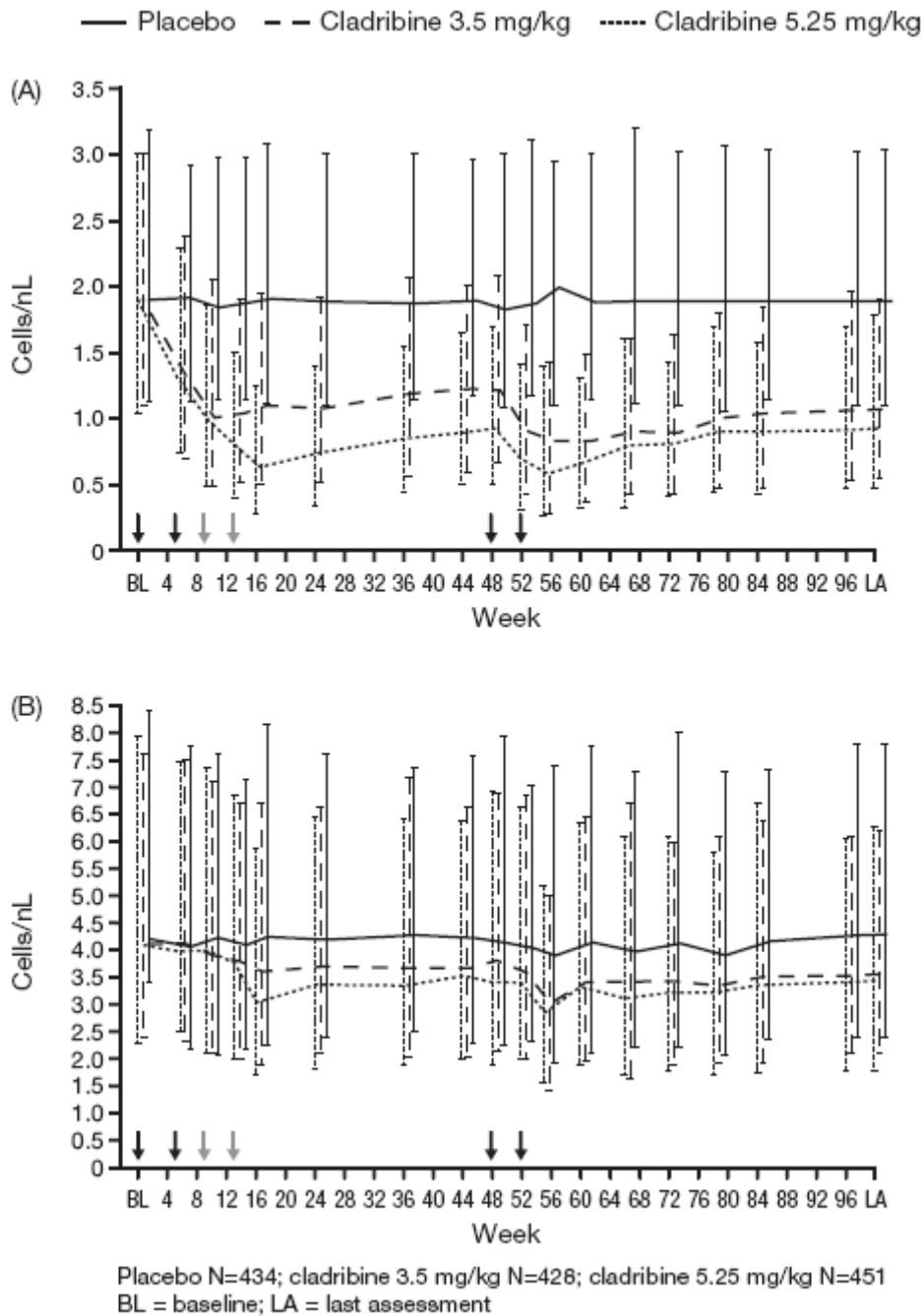
For severe events (Grade 3) attributable to the study drug, treatment could be interrupted at the discretion of the investigator until resolution to a mild/moderate event (Grade 0 or 1). This could be repeated if the Grade 3 event reoccurred, but treatment discontinuation was required for a third recurrence 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 x10⁹ /L; platelet counts of <25 x10⁹ /L; and lymphocyte counts of <0.2 x10⁹ /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



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

**SUMMARY OF MAXIMAL EFFECTS ON LYMPHOCYTE COUNTS
ACCORDING TO CTCAE LABORATORY CRITERIA**

All patients experienced reductions in their lymphocyte count as expected based on the mechanism of action of cladribine. Lymphocyte counts therefore remained within normal limits (grade 0) for only 10.2% of patients in the 3.5 mg/kg group and 4.2% in the 5.25 mg/kg group during the 96 week study vs. 83.2% of patients in the placebo group (Supplemental Table 1). Grade 3 or 4 lymphopenia occurred in 25.6% of patients in the 3.5 mg/kg group and 45.0% in the 5.25 mg/kg group, vs. 0.5% in the placebo group. The majority of the grade 4 lymphopenia incidence resulted following re-dosing of patients already experiencing grade 3 lymphopenia (this was the situation for all 3 cases of grade 4 lymphopenia in the 3.5 mg/kg group and for 9/13 cases in the 5.25 mg/kg group). The ongoing clinical development protocols have since been amended to avoid dosing subjects experiencing grade 3 lymphopenia.

Supplemental Table 1. Summary of Maximum Laboratory CTCAE grades over the 96-week Study.

Grade, n (%)	Placebo	Cladribine	Cladribine
	(N=435)	3.5 mg/kg (N=430)	5.25 mg/kg (N=454)
Haemoglobin			
0	329 (75.6)	296 (68.8)	326 (71.8)
1	88 (20.2)	101 (23.5)	112 (24.7)
2	15 (3.4)	27 (6.3)	15 (3.3)
3	3 (0.7)	5 (1.2)	1 (0.2)
4	0	0	0
Neutrophils			
0	365 (83.9)	327 (76.0)	314 (69.2)
1	34 (7.8)	52 (12.1)	81 (17.8)
2	18 (4.1)	38 (8.8)	40 (8.8)
3	12 (2.8)	5 (1.2)	14 (3.1)
4	6 (1.4)	7 (1.6)	5 (1.1)

Lymphocytes			
0	362 (83.2)	44 (10.2)	19 (4.2)
1	51 (11.7)	113 (26.3)	52 (11.5)
2	20 (4.6)	162 (37.7)	179 (39.4)
3	2 (0.5)	107 (24.9)	191 (42.1)
4	0	3 (0.7)	13 (2.9)
Platelets			
0	415 (95.4)	383 (89.1)	412 (90.7)
1	16 (3.7)	44 (10.2)	42 (9.3)
2	3 (0.7)	1 (0.2)	0
3	1 (0.2)	0	0
4	0	0	0

RELATIONSHIP BETWEEN LYMPHOCYTE COUNTS AND ZOSTER

20 patients developed herpes zoster infections (including 1 case of herpes zoster oticus): 8 patients in the 3.5 mg/kg group and 12 in the 5.25 mg/kg group. In the 3.5 mg/kg group, 5 out of the 8 patients (62.5%) experienced grade 3 or 4 lymphopenia at any time during the study, and 5 out of the 12 (41.7%) in the 5.25 mg/kg group did likewise. Herpes zoster infections therefore developed in 3.18% of cladribine tablet treated patients experiencing grade 3 or 4 lymphopenia at anytime during study compared with development in 1.75% of cladribine tablet treated patients that did not experience grade 3 or 4 lymphopenia during the study. Serial lymphocyte measurements reveal that in 70% of patients that developed zoster infection, lymphocyte counts were within grade 0, 1 or 2 at the approximate time of infection (lymphocyte counts were within grade 0, 1, 2 and 3 for 3, 3, 8 and 6 patients respectively).

Supplemental Table 2. Serious Treatment-Emergent Adverse Events Over the 96-week Study.

Data shown as number (%) patients with each event

System Organ Class Preferred Term	Cladribine			
	Placebo	Cladribine 3.5 mg/kg	5.25 mg/kg	Overall Cladribine
	(N=435)	(N=430)	(N=454)	(N=884)
Any serious adverse event	28 (6.4)	36 (8.4)	41 (9.0)	77 (8.7)
Infections and infestations	7 (1.6)	10 (2.3)	13 (2.9)	23 (2.6)
Pneumonia	3 (0.7)	3 (0.7)	3 (0.7)	6 (0.7)
Adnexitis	0	0	2 (0.4)	2 (0.2)
Appendicitis	2 (0.5)	0	0	0
Pyelonephritis	0	2 (0.5)	0	2 (0.2)
Urinary tract infection	0	1 (0.2)	1 (0.2)	2 (0.2)
Actinomycosis	0	0	1 (0.2)	1 (0.1)
Chronic sinusitis	1 (0.2)	0	0	0
Cystitis	0	0	1 (0.2)	1 (0.1)
Endometritis	0	0	1 (0.2)	1 (0.1)
Hepatitis C	1 (0.2)	0	0	0
Herpes zoster	0	1 (0.2)	0	1 (0.1)
Herpes zoster infection neurological	0	0	1 (0.2)	1 (0.1)
Herpes zoster oticus	0	0	1 (0.2)	1 (0.1)
Influenza	0	1 (0.2)	0	1 (0.1)
Lung abscess	0	0	1 (0.2)	1 (0.1)
Myocarditis bacterial	1 (0.2)	0	0	0
Orchitis	0	0	1 (0.2)	1 (0.1)
Respiratory tract infection	0	0	1 (0.2)	1 (0.1)
Salpingo-oophoritis	0	1 (0.2)	0	1 (0.1)
Subcutaneous abscess	0	1 (0.2)	0	1 (0.1)
Tuberculosis	0	0	1 (0.2)	1 (0.1)

System Organ Class Preferred Term	Cladribine			
	Placebo	Cladribine 3.5 mg/kg	5.25 mg/kg	Overall Cladribine
	(N=435)	(N=430)	(N=454)	(N=884)
Hepatobiliary disorders	3 (0.7)	3 (0.7)	6 (1.3)	9 (1.0)
Cholelithiasis	0	1 (0.2)	2 (0.4)	3 (0.3)
Hepatitis toxic	1 (0.2)	1 (0.2)	0	1 (0.1)
Cholecystitis	0	0	1 (0.2)	1 (0.1)
Cholecystitis acute	0	1 (0.2)	0	1 (0.1)
Hepatic cyst	1 (0.2)	0	0	0
Hepatitis	0	0	1 (0.2)	1 (0.1)
Hepatitis acute	0	0	1 (0.2)	1 (0.1)
Hepatosplenomegaly	0	0	1 (0.2)	1 (0.1)
Liver disorder	1 (0.2)	0	0	0
Gastrointestinal disorders	2 (0.5)	4 (0.9)	5 (1.1)	9 (1.0)
Abdominal pain upper	0	0	1 (0.2)	1 (0.1)
Colitis ulcerative	0	1 (0.2)	0	1 (0.1)
Food poisoning	1 (0.2)	0	0	0
Gastric ulcer	0	1 (0.2)	0	1 (0.1)
Gastritis erosive	0	0	1 (0.2)	1 (0.1)
Gastrointestinal motility disorder	1 (0.2)	0	0	0
Haemorrhoids	0	0	1 (0.2)	1 (0.1)
Ileus	0	0	1 (0.2)	1 (0.1)
Inguinal hernia	0	1 (0.2)	0	1 (0.1)
Nausea	0	0	1 (0.2)	1 (0.1)
Pancreatitis acute	1 (0.2)	0	0	0
Pancreatitis relapsing	1 (0.2)	0	0	0
Peritonitis	0	1 (0.2)	0	1 (0.1)
Small intestinal perforation	0	1 (0.2)	0	1 (0.1)
Toothache	0	0	1 (0.2)	1 (0.1)

System Organ Class	Cladribine			
	Placebo	Cladribine 3.5 mg/kg	5.25 mg/kg	Overall
	(N=435)	(N=430)	(N=454)	Cladribine (N=884)
Preferred Term				
Vomiting	0	0	1 (0.2)	1 (0.1)
Injury, poisoning and procedural complications	2 (0.5)	9 (2.1)	0	9 (1.0)
Ankle fracture	0	2 (0.5)	0	2 (0.2)
Fall	0	2 (0.5)	0	2 (0.2)
Concussion	0	1 (0.2)	0	1 (0.1)
Facial bones fracture	0	1 (0.2)	0	1 (0.1)
Femoral neck fracture	0	1 (0.2)	0	1 (0.1)
Femur fracture	1 (0.2)	0	0	0
Joint dislocation	0	1 (0.2)	0	1 (0.1)
Lumbar vertebral fracture	0	1 (0.2)	0	1 (0.1)
Overdose	0	1 (0.2)	0	1 (0.1)
Pneumothorax traumatic	1 (0.2)	0	0	0
Postoperative ileus	0	1 (0.2)	0	1 (0.1)
Radius fracture	0	1 (0.2)	0	1 (0.1)
Rib fracture	1 (0.2)	0	0	0
Subdural haematoma	0	1 (0.2)	0	1 (0.1)
Tibia fracture	0	1 (0.2)	0	1 (0.1)
Upper limb fracture	0	1 (0.2)	0	1 (0.1)
Wound dehiscence	0	1 (0.2)	0	1 (0.1)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	6 (1.4)	4 (0.9)	10 (1.1)

System Organ Class Preferred Term	Cladribine			
	Placebo	Cladribine 3.5 mg/kg	5.25 mg/kg	Overall Cladribine
	(N=435)	(N=430)	(N=454)	(N=884)
Uterine leiomyoma	0	3 (0.7)	2 (0.4)	5 (0.6)
Cervix carcinoma stage 0	0	0	1 (0.2)	1 (0.1)
Malignant melanoma	0	1 (0.2)	0	1 (0.1)
Myelodysplastic syndrome	0	0	1 (0.2)	1 (0.1)
Ovarian cancer	0	1 (0.2)	0	1 (0.1)
Pancreatic carcinoma metastatic	0	1 (0.2)	0	1 (0.1)
Psychiatric disorders	4 (0.9)	1 (0.2)	3 (0.7)	4 (0.5)
Suicide attempt	0	0	2 (0.4)	2 (0.2)
Completed suicide	1 (0.2)	0	0	0
Delirium	0	0	1 (0.2)	1 (0.1)
Depression	1 (0.2)	0	0	0
Intentional self-injury	1 (0.2)	0	0	0
Mental disorder	0	1 (0.2)	0	1 (0.1)
Panic attack	1 (0.2)	0	0	0
Schizophrenia, paranoid type	0	0	1 (0.2)	1 (0.1)
Cardiac disorders	4 (0.9)	1 (0.2)	2 (0.4)	3 (0.3)
Acute myocardial infarction	1 (0.2)	0	0	0
Angina pectoris	1 (0.2)	0	0	0
Arrhythmia	1 (0.2)	0	0	0
Bundle branch block left	1 (0.2)	0	0	0
Cardiac hypertrophy	1 (0.2)	0	0	0
Cardio-respiratory arrest	0	0	1 (0.2)	1 (0.1)
Cardiomyopathy	1 (0.2)	0	0	0
Myocardial infarction	0	1 (0.2)	0	1 (0.1)
Prinzmetal angina	0	0	1 (0.2)	1 (0.1)
General disorders and administration	2 (0.5)	1 (0.2)	4 (0.9)	5 (0.6)

System Organ Class Preferred Term	Cladribine			
	Placebo	Cladribine 3.5 mg/kg	5.25 mg/kg	Overall Cladribine
	(N=435)	(N=430)	(N=454)	(N=884)
site conditions				
Chest pain	1 (0.2)	0	1 (0.2)	1 (0.1)
Pyrexia	1 (0.2)	0	1 (0.2)	1 (0.1)
Asthenia	0	1 (0.2)	0	1 (0.1)
Drowning	0	0	1 (0.2)	1 (0.1)
Non-cardiac chest pain	0	0	1 (0.2)	1 (0.1)
Edema peripheral	0	0	1 (0.2)	1 (0.1)
Musculoskeletal and connective tissue disorders				
Pain in extremity	1 (0.2)	2 (0.5)	4 (0.9)	6 (0.7)
Arthritis	0	0	1 (0.2)	1 (0.1)
Bone pain	0	0	1 (0.2)	1 (0.1)
Intervertebral disc protrusion	0	1 (0.2)	0	1 (0.1)
Myalgia	0	1 (0.2)	0	1 (0.1)
Osteitis	0	0	1 (0.2)	1 (0.1)
Respiratory, thoracic and mediastinal disorders				
Dyspnea	3 (0.7)	0	4 (0.9)	4 (0.5)
Pulmonary embolism	1 (0.2)	0	2 (0.4)	2 (0.2)
Asthma	1 (0.2)	0	1 (0.2)	1 (0.1)
Asthma	0	0	1 (0.2)	1 (0.1)
Lung infiltration	0	0	1 (0.2)	1 (0.1)
Pulmonary edema	1 (0.2)	0	0	0
Nervous system disorders	2 (0.5)	2 (0.5)	2 (0.4)	4 (0.5)

System Organ Class Preferred Term	Cladribine			
	Placebo	Cladribine 3.5 mg/kg	5.25 mg/kg	Overall Cladribine
	(N=435)	(N=430)	(N=454)	(N=884)
Altered state of consciousness	0	1 (0.2)	0	1 (0.1)
Convulsion	0	1 (0.2)	0	1 (0.1)
Epilepsy	0	0	1 (0.2)	1 (0.1)
Facial spasm	1 (0.2)	0	0	0
Haemorrhagic stroke	1 (0.2)	0	0	0
Syncope	0	0	1 (0.2)	1 (0.1)
Pregnancy, puerperium and perinatal conditions				
Abortion spontaneous	2 (0.5)	2 (0.5)	2 (0.4)	4 (0.5)
Pregnancy	1 (0.2)	1 (0.2)	1 (0.2)	2 (0.2)
Ectopic pregnancy	1 (0.2)	1 (0.2)	1 (0.2)	2 (0.2)
Ectopic pregnancy	0	1 (0.2)	0	1 (0.1)
Blood and lymphatic system disorders				
Lymphopenia	0	3 (0.7)	2 (0.4)	5 (0.6)
Neutropenia	0	3 (0.7)	1 (0.2)	4 (0.5)
Neutropenia	0	1 (0.2)	1 (0.2)	2 (0.2)
Leukopenia	0	1 (0.2)	0	1 (0.1)
Pancytopenia	0	0	1 (0.2)	1 (0.1)
Thrombocytopenia	0	0	1 (0.2)	1 (0.1)
Renal and urinary disorders				
Calculus ureteric	2 (0.5)	2 (0.5)	1 (0.2)	3 (0.3)
Calculus ureteric	1 (0.2)	0	0	0
Nephrolithiasis	0	1 (0.2)	0	1 (0.1)
Nephrosclerosis	1 (0.2)	0	0	0
Renal artery stenosis	0	0	1 (0.2)	1 (0.1)
Renal colic	0	1 (0.2)	0	1 (0.1)
Renal failure chronic	0	1 (0.2)	0	1 (0.1)
Reproductive system and breast disorders				
disorders	1 (0.2)	1 (0.2)	3 (0.7)	4 (0.5)

System Organ Class Preferred Term	Cladribine			
	Placebo	Cladribine 3.5 mg/kg	5.25 mg/kg	Overall Cladribine
	(N=435)	(N=430)	(N=454)	(N=884)
Breast dysplasia	1 (0.2)	0	0	0
Menorrhagia	0	0	1 (0.2)	1 (0.1)
Metrorrhagia	0	0	1 (0.2)	1 (0.1)
Ovarian cyst	0	0	1 (0.2)	1 (0.1)
Uterine hemorrhage	0	1 (0.2)	0	1 (0.1)
Skin and subcutaneous tissue disorders	0	1 (0.2)	3 (0.7)	4 (0.5)
Hidradenitis	0	0	1 (0.2)	1 (0.1)
Lichen sclerosus	0	1 (0.2)	0	1 (0.1)
Purpura	0	0	1 (0.2)	1 (0.1)
Rash generalized	0	0	1 (0.2)	1 (0.1)
Skin reaction	0	0	1 (0.2)	1 (0.1)
Vascular disorders	1 (0.2)	0	2 (0.4)	2 (0.2)
Arterial disorder	1 (0.2)	0	0	0
Deep vein thrombosis	0	0	1 (0.2)	1 (0.1)
Hypertension	0	0	1 (0.2)	1 (0.1)
Immune system disorders	0	0	2 (0.4)	2 (0.2)
Hypersensitivity	0	0	2 (0.4)	2 (0.2)
Metabolism and nutrition disorders	1 (0.2)	0	1 (0.2)	1 (0.1)
Cachexia	0	0	1 (0.2)	1 (0.1)
Hyperglycemia	1 (0.2)	0	0	0
Hypoproteinemia	0	0	1 (0.2)	1 (0.1)
Endocrine disorders	0	0	1 (0.2)	1 (0.1)
Hyperthyroidism	0	0	1 (0.2)	1 (0.1)
Eye disorders	1 (0.2)	0	0	0
Eyelid ptosis	1 (0.2)	0	0	0

DEATHS

There were six deaths in total; four patients died during the study and two following study withdrawal (total 2 deaths from each treatment group).

During study: In the 3.5 mg/kg group, a 42-year-old, obese (120 kg) man with a history of type 2 diabetes died 8 months after his last treatment dose due to acute myocardial infarction. In the 5.25 mg/kg group, a 40-year-old man died of drowning after receiving 4 courses of treatment (4 months after his last treatment dose). Two deaths were reported in the placebo group: a 37-year-old female with a history of depression committed suicide 1 month after her last treatment and a 40-year-old female with a history of essential hypertension died of hemorrhagic stroke 8 months after her last treatment dose. All deaths during the study were considered by investigators as unlikely to be related to study medication.

Following study withdrawal: In the 3.5 mg/kg group a 61-year-old woman died of pancreatic carcinoma with liver infiltration. The diagnosis of pancreatic carcinoma in this subject was considered unlikely to be related to treatment. In the 5.25 mg/kg group, a 21-year-old female developed pancytopenia and an apparent myelodysplastic syndrome with recurrent bilateral alveolar-interstitial lung infiltrates after receiving her first and only treatment cycle of cladribine tablets (0.875 mg/kg). Six months post-treatment, she died from an acute cardiopulmonary arrest considered to be due to severe exacerbation of latent tuberculosis. At post-mortem, the chronic pathological nature of lesions in the liver and lungs suggested that the tuberculosis was long-standing and likely present in latent form prior to cladribine treatment. Cladribine therapy likely contributed to the tuberculosis reactivation. What was reported as myelodysplasia was likely reactive bone marrow changes caused by her tuberculosis infection and was probably not true myelodysplasia.

STUDY INVESTIGATORS AND OTHER PARTICIPANTS

The following people participated in the CLARITY study: **Study Steering Committee:** *Queen Mary University of London, Blizard Institute of Cell and Molecular Science, Barts and The London School of Medicine and Dentistry, Department of Neurology, Royal London Hospital, UK* – G. Giovannoni (chairperson); *Università Vita-Salute San Raffaele, Italy* – G. Comi; *University of Medicine and Dentistry New Jersey, NJ* – S. Cook; *The Ohio State University, OH, USA* – K. Rammohan; *Bamberg Hospital / University of Erlangen, Germany* – P. Rieckmann; *Danish MS Research Center, Rigshospitalet, Copenhagen, Denmark* – P. Soelberg Sørensen; *CHU de Lille, University of Lille-Nord de France, France* – P. Vermersch. **Data and Safety Monitoring Board:** M. Sandberg-Wollheim (chairperson, neurologist); *Wolfson Institute of Preventive Medicine, Queen Mary University of London, UK* – J. Cuzick

(biostatistician), *Lund University Hospital, Sweden* – G.Juliusson (hematologist); S.Reingold (multiple sclerosis expert). **CLARITY Study Group Investigators:** **Australia:** *Royal Melbourne Hospital, Victoria* – J.King; *MS Clinical Trials Research Unit, Brain and Mind Research Institute, The University of Sydney, NSW* – J.Pollard; *St. Vincent's Hospital, Melbourne, Victoria* – L.Sedal. **Austria:** *Landesnervenklinik Wagner-Jauregg, Linz* – F.Aichner; *Krankenhaus der Barmherzigen Brüder Neurologie, Linz* – C.Eggers. **Belgium:** *CHU Ourthe-Ambève, Service de Neurologie* – D.Dive; *Biomedisch Onderzoeksinstituut, Limburgs Universitair Centrum, Universiteit Hasselt, Deepenbeek* – R.Medaer. **Brazil:** *Hospital da Restauração, Ala Sul Recife* – M.Ferreira. **Bulgaria:** *UMHAT Stara Zagora EAD, Stara Zagora* – I.Manchev; *University Neurology Hospital "St. Naum", Sofia* – I.Milanov; *National Heart Hospital, Neurology Department, Special Hospital for Active, Treatment of Cardio-vascular Disease, Sofia* – L.Haralanov; *University Hospital "St. Marina", Varna* – N.Deleva; *MBAL Ruse AD, 2nd Department of Neurology, Ruse* – N.Petrova; *Medical University Pleven, 1-st base Department of Neurology, Pleven* – P.Bozhinov; *University Hospital "St. Georgi", Department of Neurology, Plovdiv* – Z.Zahariev; *University Hospital Pleven, Pleven* – B.Stamenov; *University Hospital Alexandrovska, Sofia* – P.Shotekov; *MBAL Shoumen AD, Department of Neurology, Shumen* – I.Petrov; *Military Medical Academy, Sofia* – R. Moskov. **Canada:** *Centre Hospitalier Affilié Hôpital de l'Enfant-Jésus, Quebec* – F.Émond; *Ottawa Hospital, Ottawa* – M. Freedman; *Hôpital Charles Lemoyne, Quebec* – F.Grand'Maison; *CHVO - Hôpital de Hull, Multiple Sclerosis Clinic, Quebec* – F.Jacques; *Burnaby Hospital, Vancouver Fraser Health Multiple Sclerosis Clinic* – G.Vorobeychik. **Croatia:** *University Hospital Sestre Milosrdnice, Zagreb* – V.Demarin; *General Hospital Karlovac* – M.Kovacicsek; *University Hospital Split* – I.Lusic; *General Hospital Dr Ivo Pedusic, Split* – T.Perhat-Bucevic. **Czech Republic:** *MS Center, Department of Neurology, Fakultni poliklinika, Prague* – E.Havrdova; *Neurological Department of Faculty Hospital, Hradec Králové* – R.Talab; *Faculty Hospital, Neurological Department, Olomouc* – P.Kanovsky. **Denmark:** *Danish MS Research Center, Rigshospitalitet, Copenhagen* – P.Søelberg Sørensen; *Aarhus sygehus, Scleroseklinikken, Arhus* – T.Petersen. **Estonia:** *West-Tallinn Central Hospital, MS Centre, Tallinn* – K.Gross-Paju; *Tartu University Hospital, Tartu* – I.Kalbe; *East Tallin Central Hospital, Tallinn* – T.Toomsoo. **Finland:** *University of Tampere* – I.Elovaara; *Suomen Terveystalo Clinical Research, Turku* – J-P. Eralinna; *Oulu University Hospital, Clinic of Neurology* – M.Reunanen. **France:** *Hôpital Gabriel Montpied, Clermont-Ferrand* – P.Clavelou; *Centre Hospitalier Universitaire de Nantes, Saint Herblain* – P.Damier; *CHU de Nancy – Université' de Nancy, France* – M.Debouverie; *Hôpital Pontchaillou, Rennes, France* – G.Edan; *Fondation a de Rothschild, Paris* – O.Gout; *CHU Nimes* – P.Labaugé; *Centre Hospitalier Universitaire de Nantes* – D.Laplaud, S.Wiertelwski; *CHU de Lille, University of Lille-Nord de France* – P.Vermersch. **Germany:** *Diakoniekrankenhaus Henriettenstiftung, Department of Neurology, Hannover* – F.Heidenreich; *Caritaskrankenhaus Bad Mergentheim* – M.Mäurer; *Heinrich-Heine-University, Duesseldorf* – B.Kieseier; *University Hospital Essen* – V.Limmroth; *Justus-Liebig-Universität Giessen* – P.Oschmann; *St. Joseph Hospital der Ruhr Universität Bochum, Klinik für Neurologie* – S.Schimrigk; *Klinik und Poliklinik für Neurologie, Universitätsklinikum der Universität Regensburg* – A.Steinbrecher; *University of Rostock* – U.Zettl; *Klinik für Neurologie, Goethe Universität, Frankfurt am Main* – U.Ziemann. **Greece:** *General Hospital of Athens "G. Gennimatas"* – K.Karageorgiou; *University Hospital of Ioannina* – A.Kyritsis; *Henry Dunant Hospital, Athens* – A. Papadimitriou. **Italy:** *Dip.Scienze Neurologiche e Psichiatriche, Clinica Neurologica I, Univ. degli Studi di Firenze* – M.P. Amato; *Clinica Neurologica, Università Tor Vergata, Rome* – G.Bernardi; *Dipartimento Scienze Neurologiche, Nuovo Policlinico Federico II, Napoli* – V.B.Morra; *Università Vita-Salute San Raffaele* – G. Comi; *Day Hospital Neurologia, Ospedale San Camillo* – S. Galgani; *Multiple Sclerosis Centre – Veneto Region,*

Department of Neuroscience, University Hospital of Padova – P.Gallo; Centro Sclerosi Multipla, Catania – F.Patti; Centro Sclerosi Multipla, Cagliari – M.Marrosu; S.Andrea Multiple Sclerosis Center, “La Sapienza” University, Rome – C.Pozzilli; Department of Neurological and Psychiatric Sciences, University of Bari – M.Trojano; DINOG – Dipartimento di Neuroscienze, Oftalmologia e Genetica, Università degli Studi di Genova – G.L.Mancardi. **Lebanon:** The Lebanese Hospital, Beirut – S.Gebeily; Hôpital Hotel-Dieu De France, Beirut – S.Koussa; Sahel General Hospital, Beirut – M.Wehebe; American University of Beirut – B.Yamout. **Lithuania:** Kaunas Medical University Hospital – A.Vaitkus. **Latvia:** Vecmilgravis Hospital, Riga – M.Metra. **Morocco:** CHU Hassan II, Department of Neurology, Fes – O.Messouak; Service de Neurologie, Hôpital Militaire MOHAMED V, Rabat – R.Mossaddaq; CHU Ibn Rochd, Casablanca – I.Slassi; Hopital des specialites Rabat – M.Yahyaoui. **The Netherlands:** Academic MS Center Sittard, Sittard-Geleen – R.M.M. Hupperts. **Poland:** 2nd Department of Neurology, Institute of Psychiatry and Neurology, Warsaw – A.Czlonkowska; Neurology Clinic, Medical Academy in Pozna, Poznan – W. Kozubski; Neurology Clinic, Medical Academy in Gdansk – W.Nyka; Department of Neurology, Medical University of Lodz – K.Selmaj; Jagiellonian University Medical College, Krakow – A.Szczudlik. **Portugal:** Hospital de S.Marcos, Serviço de Neurologia, Bragal – J.Figueiredo; Hospital dos Capuchos, Serviço de Neurologia, Lisbon – R.Pedrosa. **Russia:** Siberian State Medical University, Tomsk – V.Alifirova; Rostov State Medical University, Rostov-on-Don – V.Balyazin; Kemerovo State Medical Academy, Kemerovo – O.Barbarash; Municipal Medical Unit, “City Hospital #33”, Nizhny Novgorod – A.Belova; Russian State Medical University & Moscow MS Centre, Moscow – A.Boyko, E.Gusev; Clinical Hospital #122 of Medical Biological Federal Agency Russian Federation, St.Petersburg – A.Elchaninov; Kazan State Medical University, Kazan – E.Jacoupov; Medical Academy of Postgraduate Education, Clinic and Chair of Neurology, St. Petersburg – N.Julev; Moscow Regional Scientific Research, Clinical Institute named after M. F. Vladimirsky, Moscow – S.Kotov; Vladimir Regional Clinical Hospital, Institution of Public Health, Vladimir – A.Kudryavtsev; Kursk Regional Clinical Hospital, Kursk – V.Laskov; Sverdlovsk Regional Clinical Hospital, Ekaterinburg – O.Lesnyak; Military Medical Academy named after S.M.Kirov of Department of Defense of Russian Federation, Clinic of Neurology, St.Petersburg – M.Odinak; Kaluga Regional Hospital, Kaluga – E.Pasechnik; Samara State Medical University – I.Poverennonva; St.Petersburg State Medical, University named after I.P.Pavlov, University – A.Skoromets; Yaroslavl State Medical Academy Department of Diseases of Nervous System, Yaroslavl – N.Spirin; Institute of Human Brain of Russian Academy of Science, St.Petersburg – I.Stolyarov; Rehabilitological department of neurological disorders of Central Clinical Hospital #2, n.a. Semashko of OAO RZD, Moscow – O.Vorobieva; Saratov State Medical University, Saratov – O.Voskresenskaya; St.Petersburg Region Clinical Hospital – L. Zaslavskiy; State Institution Science Research Institute of Clinical and Experimental Lymphology, Novosibirsk – E.Zonova. **Saudi Arabia:** King Faisal Specialist Hospital and Research Centre – S.Bohlega; King Abdullah International Medical Research Centre & King Saud Bin Abdulaziz University for Health Sciences, Riyadh – M.El-Jumah. **Serbia and Montenegro:** Institute of Neurology Clinical Center of Serbia, Belgrade – J.Drulovic; Clinic of Neurology, Clinical Centre Vojvodina, Novi Sad – C.Nadj. **Switzerland:** University Hospital Zurich – N.Goebels; Centre Hospitalier Universitaire Vaudois, Lausanne – M.Schluep; **Tunisia:** Hôpital Fattouma Bourghiba Monastir – M.Ayed-Frih; Institut National de Neurologie, Tunis – F.Hentati; Hôpital Bourguiba, Sfax – C.Mhiri; Hôpital Charles Nicolle – A. Mrabet; Hôpital Militaire de Tunis – R.Mrissa. **Turkey:** 9 Eylül University Medical School, Izmir – E.Idiman; Hacettepe University Tıp Fakultesi, Ankara – R. Karabudak; Uludag University Medical School, Bursa – O.F.Turan. **UK:** Department of Neurology, Hull Royal Infirmary, Hull – Fayyaz Ahmed; Queen’s Medical Centre, Division of Clinical Neurology, University of Nottingham – C.Constantinescu; Queen Mary University of London, Blizard Institute of Cell

*and Molecular Science, Barts and The London School of Medicine and Dentistry, Department of Neurology, Royal London Hospital – G.Giovanoni; Keele University, University Hospital of North Staffordshire, Stoke-on-Trent – C.Hawkins; Multiple Sclerosis Group, Department of Neurology, John Radcliffe Hospital, Oxford – J.Palace; Royal Hallamshire Hospital, Sheffield – B.Sharrack. **Ukraine:** Institute for Clinical Radiology, Research Centre for Radiation Medicine, Academy of Medical Sciences of Ukraine, Kyiv – K.Loganovsky; Vinnytsya Regional Psychoneurological Hospital, Department of Neurology, Vinnytsia National Medical University, Vinnytsya – S.Moskovko; Lviv Regional Central Hospital, Department of Neurology, Lviv State Medical University, Lviv, Ukraine – T.Nehrych; Institute of Neurology, Psychiatry and Narcology of the AMS Ukraine, Kharkiv – N.P.Voloshyna. **USA:** Medford Neurological & Spine Clinic, Medford, OR – W.Carlini; University of Medicine and Dentistry New Jersey, NJ – S.Cook; MS Center of Atlanta, Atlanta, GA – J.English; Alpine Clinical Research Center, Boulder, CO – G.Garmany; [No affiliation], USA – S.Glyman; Neurology & Neurosurgery Associates of Tacoma PLLC, Tacoma, WA – J.Huddlestone; Duke University Medical Center, NC – B.Hurwitz; Capitol Neurology, Charlestown, WV – K.Kresa-Reahl; [Merck Serono] – D.Mikol; MS Center of Oklahoma, Merci Neuroscience Institute, OK – G.Pardo; The Ohio State University, OH – K.Rammohan; Neurology Consultants of the Carolinas, NC – H.Rao; Minor & James Medical, PLLC, Seattle, WA – M.Reif; Shepherd Center, Inc, Atlanta, GA – B.Thrower; Maryland Center for MS Neurology, Baltimore, MD – W.Royal; Neurological Associates of Tulsa, Inc., Tulsa, OK – R.Webb; Consultants in Neurology Ltd, Northbrook, IL – D.Wynn, C.Naga, N.Allen, K.Lin; Rush University Medical Center, Chicago, IL – D.Stefoski, R.Balabanov.*