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Safety and tolerability of cladribine tablets in multiple sclerosis: the CLARITY (CLAdRibine Tablets treating multiple sclerosis orally) study

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SJ Greenberg⁸, on behalf of the CLARITY Study Group*

Abstract

Background: Cladribine is a synthetic deoxyadenosine analogue in development as an oral multiple sclerosis (MS) therapy.

Objective: To report in detail the safety findings from the 96-week, phase III, double-blind CLARITY study, which evaluated treatment with cladribine tablets in relapsing–remitting MS.

Methods: A total of 1,326 patients were randomized 1 : 1 : 1 to two short-course regimens of cladribine tablets (3.5 or 5.25 mg/kg cumulative dose over 96 weeks) or placebo. Safety assessments included monitoring for adverse events (AEs), routine physical and neurologic examinations and frequent laboratory parameter assessments.

Results: Of the randomized patients, 88.6% completed treatment with cladribine tablets versus 86.3% with placebo. Lymphopenia was the most commonly reported AE in patients treated with cladribine tablets and was anticipated based on the mechanism of action. The incidence of infections was 48.3% with cladribine tablets and 42.5% with placebo, with 99.1% and 99.0% rated mild-to-moderate by investigators. Herpes zoster infections developed in 20 (2.3%) cladribine-treated patients; all cases were dermatomal. There were no herpes zoster infections in the placebo group. Nine (1.0%) patients experienced events related to uterine leiomyomas in the cladribine tablets groups versus one (0.2%) with placebo. Three isolated cases of malignancy were reported in cladribine-treated patients during the study; a fourth was reported during post-study surveillance. A pre-malignant cervical carcinoma in situ was also reported. The incidence of malignancies during the study did not exceed the expected rate in a population standardized for country, gender and age.

Conclusion: The safety and tolerability profile observed in the CLARITY study together with the reported efficacy support the potential for cladribine tablets as an MS therapy.

Keywords

Cladribine tablets, disease-modifying therapy, lymphopenia, multiple sclerosis, randomized controlled trial, safety, short-course therapy

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Introduction

Cladribine (2-chlorodeoxyadenosine; 2-CdA) is a synthetic analogue of deoxyadenosine that preferentially reduces circulating T and B lymphocytes, providing targeted and sustained effects, which permit administration in an intermittent short-course dosing regimen.¹ The immunologic action of cladribine suggested that it may be beneficial in the treatment of autoimmune diseases such as MS, in which T and B lymphocytes are thought to be key inflammatory mediators.²

In the 1990s, phase II and III clinical trials of parenteral cladribine in progressive and relapsing forms of MS showed significant effects on clinical and/or MRI outcomes accompanied by an acceptable safety and tolerability profile.^{3–6} An oral formulation of cladribine was subsequently developed – cladribine tablets – and is currently in late-stage development for the treatment of relapsing forms of MS. Key efficacy and safety results from the 96-week, phase III, double-blind CLARITY (CLAdRIbine Tablets treating multiple sclerosis orally) study in patients with relapsing-remitting MS have been reported.⁷ Here we further report the evaluation of the safety findings from this study, focusing on events of special interest, including effects on the hematologic system, infections, neoplasms (both malignant and benign) and pregnancies.

Methods

Patients

Patients were recruited from 155 clinical centers in 32 countries. An overview of eligibility criteria has been reported.⁷ Specific enrolment criteria relating to safety were as follows: females had to be willing to use contraception for the duration of the study or be post-menopausal or surgically sterilized. Pregnant or breastfeeding females were excluded from the study. Males had to be willing to use contraception to avoid pregnancies in their partners. Patients were excluded from the study if they had a history of malignancy; had a history of persistent anemia, leukopenia, neutropenia, or thrombocytopenia after immunosuppressive therapy; had abnormal hematologic laboratory tests within 28 days of study entry; had systemic disease that might interfere with their safety, compliance or evaluation; or had compromised immune function or any infection at the time of screening.

Study design and treatment

This was a 96-week, randomized, double-blind, placebo-controlled study, with two 48-week treatment periods. Patients were randomized (1 : 1 : 1) to one of two dosing

regimens of cladribine tablets (cumulative dose of 3.5 or 5.25 mg/kg over 96 weeks), or matching placebo. In the first 48 weeks, treatments were administered as four short courses, consisting of one or two 10-mg cladribine tablets or matching placebo, given once daily for four or five consecutive days at 4-week intervals starting at weeks 1, 5, 9 and 13. In the placebo group, patients received four courses of placebo; in the cladribine 3.5 mg/kg group, patients received two courses of cladribine tablets followed by two courses of placebo; and in the cladribine 5.25 mg/kg group, patients received four courses of cladribine tablets. In the second 48 weeks, patients received two short courses of cladribine tablets (both cladribine groups) or placebo, starting at weeks 48 and 52. This corresponded to 8–20 days of active treatment in the first 48 weeks, and to 8–10 days of treatment in the second 48 weeks. Rescue therapy with subcutaneous interferon beta-1a 44 µg (three times per week) was available after week 24, if a patient experienced more than one relapse and/or a sustained increase in Expanded Disability Status Scale (EDSS) score. Details of blinding are reported elsewhere.⁷

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. All patients participating in the study provided written informed consent. For sites in the USA, a patient authorization under Health Insurance Portability and Accountability Act (HIPAA) was also obtained. ClinicalTrials.gov identifier: NCT00213135, EudraCT number: 2004-005148-28.

Study procedures and assessments

Safety assessments included monitoring for adverse events (AEs), serious AEs (SAEs), physical examination and laboratory parameters. AEs were recorded at the pre-study evaluation, and throughout the study from day 1 to week 96 at each study visit or whenever they were reported. The severity of AEs was rated by the site investigators as mild (patient aware of the event or symptom but the event or symptom was easily tolerated); moderate (patient experienced sufficient discomfort to interfere with or reduce his or her usual level of activity); or severe (significant impairment of functioning occurred, i.e. the patient was unable to carry out usual activities and/or the patient's life was at risk from the event). Laboratory results were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. An SAE was defined as any AE that resulted in death; was life-threatening; required inpatient hospitalization or prolonged existing hospitalization; was a congenital anomaly or birth defect; resulted in persistent or significant disability or incapacity; or was otherwise considered as medically important.

Physical examinations were performed at the pre-study evaluation, day 1, week 48 and week 96. Clinical laboratory tests, including chemistry, hematology and urinalysis, were performed at the pre-study evaluation, day 1, and weeks 5, 9, 13, 16, 24, 36, 44, 48, 52, 60, 72, 84 and 96 (hematology analysis was also performed at weeks 2, 55, 66 and 78). Abnormal laboratory findings were not routinely reported as AEs unless they were judged by the investigators as clinically significant changes from baseline values, met criteria for an SAE, resulted in discontinuation of treatment and/or required medical intervention.

Withdrawal from the trial was mandatory in the following situations: initiation of treatment with another investigational drug; non-compliance; and major protocol violation. The site investigator was able to withdraw a patient at any time if this was considered to be in the patient's best interest. Treatment was automatically discontinued in any patient who became pregnant and the patient was encouraged to be followed up for safety observations. Patients who discontinued trial medication for any reason, including those meeting the criteria for rescue medication, were encouraged to continue with all trial assessments. Patients not wishing to continue with trial assessments were asked to complete a week 96/early termination visit.

Patient safety data was reviewed by an independent Data Safety Monitoring Board (DSMB), which met at least three times annually during the course of the study. The Board was charged with assessing safety in an ongoing fashion throughout the study and with recommending study changes based on safety considerations and risk-benefit assessments if needed.

Management of hematologic abnormalities

If a Grade 3 hematologic abnormality developed, subsequent resolution to a normal laboratory value

(Grade 0) or to a Grade 1 abnormality was required prior to re-treatment. Re-treatment could be delayed or interrupted for up to four weeks until resolution was obtained. However, treatment discontinuation was required for a Grade 3 abnormality that did not resolve beyond a 4-week treatment interruption. In addition, treatment discontinuation was mandated by the study protocol for a third recurrence of a Grade 3 hematologic abnormality or for the occurrence of any Grade 4 abnormality, with the exception of lymphopenia (the intended pharmacologic effect of cladribine treatment), which was managed at the discretion of the investigators. The threshold levels for Grade 1–4 hematologic abnormalities are listed in Table 1.

Statistics

The intent-to-treat (ITT) population included all patients who were randomized into the trial. All patients who received at least one administration of study medication with a safety follow-up assessment were included in the safety population. All AEs were coded into standardized medical terminology using version 11.0 of the Medical Dictionary for Regulatory Activities (MedDRA) and were summarized for each treatment group by system organ class and preferred term. Additional summaries were presented by treatment period (weeks 0–48 versus weeks 48–96), by severity and by relationship to study drug (as assessed by the investigators). Patients who prematurely withdrew from the study were summarized by primary withdrawal reason for each treatment group. Vital signs and laboratory tests at baseline and change from baseline were examined descriptively and summarized by treatment group.

Table 1. Threshold levels for Grade 1–4 hematologic abnormalities

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin	<13.0–10.0 g/dL <8.1–6.2 mmol/L <130–100 g/L	<10.0–8.0 g/dL <6.2–4.9 mmol/L <100–80 g/L	<8.0–6.5 g/dL <4.9–4.0 mmol/L <80–65 g/L	<6.5 g/dL <4.0 mmol/L <65 g/L
Leukocytes	<4,100–3,000/mm ³ <4.1–3.0 × 10 ⁹ /L	<3,000–2,000/mm ³ <3.0–2.0 × 10 ⁹ /L	<2,000–1,000/mm ³ <2.0–1.0 × 10 ⁹ /L	<1,000/mm ³ <1.0 × 10 ⁹ /L
Lymphocytes	<1,000–800/mm ³ <1.0–0.8 × 10 ⁹ /L	<800–500/mm ³ <0.8–0.5 × 10 ⁹ /L	<500–200/mm ³ <0.5–0.2 × 10 ⁹ /L	<200/mm ³ <0.2 × 10 ⁹ /L
Neutrophils	<2,000–1,500/mm ³ <2.0–1.5 × 10 ⁹ /L	<1,500–1,000/mm ³ <1.5–1.0 × 10 ⁹ /L	<1,000–500/mm ³ <1.0–0.5 × 10 ⁹ /L	<500/mm ³ <0.5 × 10 ⁹ /L
Platelets	<140,000–75,000/mm ³ <140–75.0 × 10 ⁹ /L	<75,000–50,000/mm ³ <75.0–50.0 × 10 ⁹ /L	<50,000–25,000/mm ³ <50.0–25.0 × 10 ⁹ /L	<25,000/mm ³ <25.0 × 10 ⁹ /L

Epidemiologic analysis of malignancies

A standardized incidence ratio (SIR) was calculated in a post-hoc analysis to compare the observed number of cancers during study with the expected number obtained by applying the rates from a reference population to the CLARITY population standardized for country, gender and age.⁸ The SIR was obtained by dividing the number of observed cases by the number of expected cases. A mid-P 95% confidence interval of the SIR was calculated using *Episheet* (Rothman K *Episheet*, version 2005: Spreadsheets for the analysis of epidemiologic data). The *Cancer Incidence in Five Continents Vol. IX* was used as the reference for the cancer incidence rates (1998–2002).⁹ For five countries where no data were available, incidence rates from similar countries were used. Choice of these countries was based on geographic and cultural proximity.¹⁰

Results

Patient disposition

The ITT population comprised 1,326 patients (placebo, $n=437$; cladribine 3.5 mg/kg, $n=433$; and cladribine 5.25 mg/kg, $n=456$) and was generally well balanced across the three treatment groups in terms of demographics and disease characteristics.⁷ The safety population comprised 1,319 patients (placebo, $n=435$; cladribine 3.5 mg/kg, $n=430$; cladribine 5.25 mg/kg, $n=454$).

Of the ITT population, 86.3%, 91.2%, and 86.2% of patients completed treatment in the placebo, cladribine 3.5 mg/kg and 5.25 mg/kg groups, respectively, with a total of 161 patients (12.1%) discontinuing before completion. Principal reasons for withdrawing prematurely from treatment included AEs, perceived lack of efficacy/disease progression, protocol violation and loss to follow-up (Table 2). In the placebo and cladribine 3.5 mg/kg and 5.25 mg/kg treatment groups, 2.1%, 3.5%, and 7.9% of patients, respectively, withdrew from treatment due to AEs and 5.5%, 1.2%, and 1.1% of patients, respectively, withdrew due to perceived lack of efficacy/disease progression. Patient-years of treatment exposure were 392.9, 404.7 and 410.2 in the placebo, cladribine 3.5 mg/kg and 5.25 mg/kg groups, respectively.

Safety overview

Of the safety population, 1,047 patients reported a total of 7,184 AEs during the study: in the placebo group, 319 (73.3%) patients experienced 1,958 AEs; in the cladribine 3.5 mg/kg group, 347 (80.7%) patients experienced 2,514 AEs; and in the cladribine 5.25 mg/kg

group, 381 (83.9%) patients experienced 2,712 AEs (Table 3). The most common AEs that showed at least two-fold treatment group differences are presented in Table 4. AEs with an incidence in the cladribine 5.25 mg/kg group that was more than 1% greater than that in both the 3.5 mg/kg and placebo groups, suggesting the possibility of a dose-relationship, were lymphopenia, leukopenia, lymphocyte count decreased, vertigo, tinnitus and hypesthesia.

Treatment discontinuations due to AEs

Of the 1,319 patients in the safety population, 60 (4.5%) discontinued treatment due to an AE: nine (2.1%) in the placebo group, 15 (3.5%) in the cladribine 3.5 mg/kg group and 36 (7.9%) in the cladribine 5.25 mg/kg group. The most common AEs leading to treatment discontinuation were 'lymphopenia' and 'lymphocyte count decreased/abnormal' and involved 20 patients (four [0.9%] in the cladribine 3.5 mg/kg group and 16 [3.5%] in the 5.25 mg/kg group). In addition, three (0.7%) patients in the cladribine 5.25 mg/kg group discontinued treatment due to leukopenia. None of the patients treated with placebo withdrew from treatment due to lymphopenia or leukopenia (Table 5). When discontinuations due to pregnancies, lymphopenia (including lymphocyte count decreased/abnormal) and leukopenia were excluded, treatment was discontinued due to the remaining AEs in 6 (1.4%), 11 (2.6%) and 13 (2.9%) patients in the placebo, cladribine 3.5 mg/kg and 5.25 mg/kg groups, respectively. Other types of AEs leading to treatment discontinuation included infections and infestations (placebo group $n=2$ [0.5%], cladribine groups $n=5$ [0.6%]); hepatobiliary disorders (placebo group $n=1$ [0.2%], cladribine groups $n=3$ [0.3%]); neoplasms – benign, malignant and unspecified (placebo group $n=0$, cladribine groups $n=4$ [0.5%]); and skin and subcutaneous disorders (placebo group $n=0$, cladribine groups $n=4$ [0.5%]).

SAEs and deaths

During the 96-week trial, 105 patients experienced 185 SAEs. In the placebo, cladribine 3.5 mg/kg and 5.25 mg/kg groups, respectively, 28 (6.4%) patients experienced 44 SAEs, 36 (8.4%) patients experienced 61 SAEs and 41 (9.0%) patients experienced 80 SAEs (Table 6). One patient in the 5.25 mg/kg group was reported to have experienced 19 SAEs including an exacerbation of tuberculosis, which was probably present, although not detected, prior to cladribine treatment. This case is discussed in more detail below.

SAEs by system organ class that were reported in more than 1% of patients in a treatment group and were at least twice as common in a cladribine treatment

Table 2. Reasons for withdrawing prematurely from treatment^a

	Placebo (n = 437)	Cladribine 3.5 mg/kg (n = 433)	Cladribine 5.25 mg/kg (n = 456)	Cladribine overall (n = 889)
Patients, n (%)				
Completed treatment	377 (86.3)	395 (91.2)	393 (86.2)	788 (88.6)
Discontinued treatment	60 (13.7)	38 (8.8)	63 (13.8)	101 (11.4)
Reasons for premature treatment withdrawal				
Adverse event	9 (2.1)	15 (3.5)	35 (7.7)	51 (5.7)
Perceived lack of efficacy/disease progression	24 (5.5)	5 (1.2)	5 (1.1)	10 (1.1)
Protocol violation	9 (2.1)	5 (1.2)	5 (1.1)	10 (1.1)
Loss to follow-up	3 (0.7)	2 (0.5)	4 (0.9)	6 (0.7)
Death	2 (0.5)	1 (0.2)	1 (0.2)	2 (0.2)
Other ^b	13 (3.0)	10 (2.3)	13 (2.9)	23 (2.6)

^aITT population.^bOther reasons for treatment discontinuation in the placebo and cladribine 3.5 and 5.25 mg/kg groups include employment; move out of state/country; cannot visit site regularly; randomized by mistake; wanted other treatment; family circumstances; wanted to start a family; felt worse since study start; personal decision/no reason provided.**Table 3.** Safety overview

	Placebo (n = 435)	Cladribine 3.5 mg/kg (n = 430)	Cladribine 5.25 mg/kg (n = 454)	Cladribine overall (n = 884)
Patients, n (%)				
Any AE	319 (73.3)	347 (80.7)	381 (83.9)	728 (82.4)
Most common AEs ^a				
Headache	75 (17.2)	104 (24.2)	94 (20.7)	198 (22.4)
Lymphopenia	8 (1.8)	93 (21.6)	143 (31.5)	236 (26.7)
Nasopharyngitis	56 (12.9)	62 (14.4)	58 (12.8)	120 (13.6)
URTI	42 (9.7)	54 (12.6)	52 (11.5)	106 (12.0)
Nausea	39 (9.0)	43 (10.0)	50 (11.0)	93 (10.5)
AEs leading to treatment discontinuation	9 (2.1)	15 (3.5)	36 (7.9)	51 (5.8)
AEs leading to study withdrawal	5 (1.1)	5 (1.2)	10 (2.2)	15 (1.7)
Serious AEs	28 (6.4)	36 (8.4)	41 (9.0)	77 (8.7)
Deaths	2 (0.5)	2 (0.5)	2 (0.4)	4 (0.4)
Events, n (%)	(n = 1,958)	(n = 2,514)	(n = 2,712)	(n = 5,226)
Any AE	1,958 (100)	2,514 (100)	2,712 (100)	5,226 (100)
Most common AEs				
Headache	189 (9.7)	264 (10.5)	265 (9.8)	529 (10.1)
Lymphopenia	11 (0.6)	123 (4.9)	195 (7.2)	318 (6.1)
Nasopharyngitis	95 (4.9)	107 (4.3)	91 (3.4)	198 (3.8)
URTI	80 (4.1)	118 (4.7)	100 (3.7)	218 (4.2)
Nausea	49 (2.5)	74 (2.9)	69 (2.5)	143 (2.7)

AE = adverse event; URTI = upper respiratory tract infection.

^aReported by ≥10% of patients in any group.

group compared with placebo were gastrointestinal disorders (0.5%, 0.9% and 1.1% of patients in the placebo, cladribine 3.5 mg/kg and 5.25 mg/kg groups, respectively); injury, poisoning and procedural complications (0.5%, 2.1% and 0%, respectively); and neoplasms – benign, malignant and unspecified (0%, 1.4% and 0.9%, respectively; Table 6). Individual

SAEs that were reported in more than 0.5% of patients in a treatment group and were at least twice as common in a cladribine treatment group compared with placebo were lymphopenia (0%, 0.7% and 0.1% of patients in the placebo, cladribine 3.5 mg/kg and 5.25 mg/kg groups, respectively) and SAEs related to uterine leiomyoma (0%, 0.7% and 0.4%, respectively; Table 6).

Table 4. Adverse events reported in $\geq 1\%$ patients in any treatment group that show two-fold treatment differences^a

System organ class Preferred term, ^b n (%)	Placebo (n = 435)	Cladribine 3.5 mg/kg (n = 430)	Cladribine 5.25 mg/kg (n = 454)	Cladribine overall (n = 884)
Blood and lymphatic system disorders				
Lymphopenia	8 (1.8)	93 (21.6)	143 (31.5)	236 (26.7)
Leukopenia	3 (0.7)	24 (5.6)	39 (8.6)	63 (7.1)
Neutropenia	2 (0.5)	8 (1.9)	10 (2.2)	18 (2.0)
Anemia	2 (0.5)	5 (1.2)	5 (1.1)	10 (1.1)
Investigations				
Lymphocyte count decreased	0	13 (3.0)	26 (5.7)	39 (4.4)
White blood cell count decreased	0	3 (0.7)	7 (1.5)	10 (1.1)
Body temperature increased	5 (1.1)	2 (0.5)	2 (0.4)	4 (0.5)
Ear and labyrinth disorders				
Vertigo	11 (2.5)	14 (3.3)	23 (5.1)	37 (4.2)
Tinnitus	2 (0.5)	2 (0.5)	10 (2.2)	12 (1.4)
General disorders and administration site conditions				
Pyrexia	8 (1.8)	14 (3.3)	18 (4.0)	32 (3.6)
Gait disturbance	2 (0.5)	2 (0.5)	5 (1.1)	7 (0.8)
Hyperthermia	2 (0.5)	5 (1.2)	1 (0.2)	6 (0.7)
Pain	5 (1.1)	2 (0.5)	3 (0.7)	5 (0.6)
Skin and subcutaneous tissue disorders				
Alopecia	5 (1.1)	15 (3.5)	14 (3.1)	29 (3.3)
Rash	5 (1.1)	10 (2.3)	11 (2.4)	21 (2.4)
Dermatitis allergic	3 (0.7)	12 (2.8)	6 (1.3)	18 (2.0)
Acne	2 (0.5)	7 (1.6)	2 (0.4)	9 (1.0)
Infections and infestations				
Viral upper respiratory tract infection	5 (1.1)	13 (3.0)	7 (1.5)	20 (2.3)
Herpes zoster ^c	0	8 (1.9)	12 (2.6)	20 (2.3)
Vaginal infection	1 (0.2)	8 (1.9)	5 (1.1)	13 (1.5)
Viral infection	2 (0.5)	6 (1.4)	6 (1.3)	12 (1.4)
Respiratory tract infection viral	2 (0.5)	6 (1.4)	5 (1.1)	11 (1.2)
Vulvovaginal mycotic infection	2 (0.5)	1 (0.2)	6 (1.3)	7 (0.8)
Tooth abscess	3 (0.7)	1 (0.2)	5 (1.1)	6 (0.7)
Tonsillitis	6 (1.4)	0	4 (0.9)	4 (0.5)
Injury, poisoning and procedural complications				
Contusion	3 (0.7)	6 (1.4)	9 (2.0)	15 (1.7)
Ankle fracture	5 (1.1)	4 (0.9)	2 (0.4)	6 (0.7)
Joint sprain	6 (1.4)	3 (0.7)	1 (0.2)	4 (0.5)
Procedural pain	7 (1.6)	0	2 (0.4)	2 (0.2)
Nervous system disorders				
Hypesthesia	4 (0.9)	2 (0.5)	9 (2.0)	11 (1.2)
Syncope	3 (0.7)	6 (1.4)	5 (1.1)	11 (1.2)
Somnolence	6 (1.4)	3 (0.7)	6 (1.3)	9 (1.0)
Paresthesia	2 (0.5)	4 (0.9)	5 (1.1)	9 (1.0)
Migraine	8 (1.8)	4 (0.9)	4 (0.9)	8 (0.9)
Radiculopathy	5 (1.1)	0	0	0
Reproductive system and breast disorders				
Dysmenorrhea	3 (0.7)	7 (1.6)	4 (0.9)	11 (1.2)
Metrorrhagia	1 (0.2)	1 (0.2)	5 (1.1)	6 (0.7)

(continued)

Table 4. Continued

System organ class Preferred term, ^b n (%)	Placebo (n = 435)	Cladribine 3.5 mg/kg (n = 430)	Cladribine 5.25 mg/kg (n = 454)	Cladribine overall (n = 884)
Cardiac disorders				
Angina pectoris	3 (0.7)	6 (1.4)	5 (1.1)	11 (1.2)
Gastrointestinal disorders				
Dry mouth	1 (0.2)	4 (0.9)	6 (1.3)	10 (1.1)
Gastritis	9 (2.1)	3 (0.7)	5 (1.1)	8 (0.9)
Periodontitis	3 (0.7)	6 (1.4)	2 (0.4)	8 (0.9)
Flatulence	1 (0.2)	2 (0.5)	5 (1.1)	7 (0.8)
Gastritis erosive	5 (1.1)	1 (0.2)	1 (0.2)	2 (0.2)
Respiratory, thoracic and mediastinal disorders				
Dyspnea	4 (0.9)	1 (0.2)	8 (1.8)	9 (1.0)
Rhinorrhea	2 (0.5)	3 (0.7)	6 (1.3)	9 (1.0)
Eye disorders				
Conjunctivitis	2 (0.5)	3 (0.7)	6 (1.3)	9 (1.0)
Vision blurred	2 (0.5)	5 (1.2)	0	5 (0.6)
Renal and urinary disorders				
Dysuria	2 (0.5)	4 (0.9)	5 (1.1)	9 (1.0)
Neoplasms benign, malignant and unspecified (including cysts and polyps)				
Uterine leiomyoma	1 (0.2)	5 (1.2)	4 (0.9)	9 (1.0)
Musculoskeletal and connective tissue disorders				
Muscle spasms	5 (1.1)	2 (0.5)	6 (1.3)	8 (0.9)
Vascular disorders				
Hot flush	1 (0.2)	1 (0.2)	5 (1.1)	6 (0.7)

^aAEs for which the percentage of patients in one active treatment group is $\geq 2 \times$ the percentage of patients in the placebo group, or the percentage of patients in the placebo group is $\geq 2 \times$ the percentage of patients in the active treatment group.

^bMedical Dictionary for Regulatory Activities (MedDRA) v11.0 terminology.

^cIncludes one case of herpes zoster oticus (Ramsay-Hunt syndrome) reported in the cladribine 5.25 mg/kg group.

Table 5. Adverse events leading to treatment discontinuation of ≥ 2 patients

Preferred term, n (%)	Placebo (n = 435)	Cladribine 3.5 mg/kg (n = 430)	Cladribine 5.25 mg/kg (n = 454)	Cladribine overall (n = 884)
Any AE leading to treatment discontinuation	9 (2.1)	15 (3.5)	36 (7.9)	51 (5.8)
Lymphopenia	0	2 (0.5)	9 (2.0)	11 (1.2)
Leukopenia	0	0	3 (0.7)	3 (0.3)
Lymphocyte count decreased	0	1 (0.2)	6 (1.3)	7 (0.8)
Lymphocyte count abnormal	0	1 (0.2)	1 (0.2)	2 (0.2)
Pregnancy	3 (0.7)	0	4 (0.9)	4 (0.5)

There were four deaths during the study and two deaths after patients were withdrawn from study (withdrawals had been due to AEs); the six deaths were equally distributed across the three treatment groups (Table 3). Causes of death during the study were suicide (placebo), hemorrhagic stroke (placebo), acute myocardial infarction (cladribine 3.5 mg/kg) and drowning (cladribine 5.25 mg/kg). Causes of death following study withdrawal were metastatic

pancreatic carcinoma (cladribine 3.5 mg/kg group) and acute cardiopulmonary arrest (cladribine 5.25 mg/kg).

The details on the metastatic pancreatic carcinoma are as follows: a 61-year-old woman in the 3.5 mg/kg group discontinued from the study following her scheduled week 72 visit due to a spectrum of gastrointestinal and constitutional complaints. She was subsequently diagnosed with metastatic pancreatic carcinoma and

Table 6. Serious adverse events

Patients, <i>n</i> (%)	Placebo (<i>n</i> = 435)	Cladribine 3.5 mg/kg (<i>n</i> = 430)	Cladribine 5.25 mg/kg (<i>n</i> = 454)	Cladribine overall (<i>n</i> = 884)
Any SAE	28 (6.4)	36 (8.4)	41 (9.0)	77 (8.7)
Most common ^a SAEs that show treatment differences ^b by system organ class				
Neoplasms – benign, malignant and unspecified	0	6 (1.4)	4 (0.9)	10 (1.1)
Gastrointestinal disorders	2 (0.5)	4 (0.9)	5 (1.1)	9 (1.0)
Injury, poisoning and procedural complications	2 (0.5)	9 (2.1)	0	9 (1.0)
Most common ^c SAEs that show treatment differences ^b by preferred term				
Uterine leiomyoma	0	3 (0.7)	2 (0.4)	5 (0.6)
Lymphopenia	0	3 (0.7)	1 (0.1)	4 (0.5)
Events, <i>n</i> (%)	(<i>n</i> = 1,958)	(<i>n</i> = 2,514)	(<i>n</i> = 2,712)	(<i>n</i> = 5,226)
Any SAE	44 (2.2)	61 (2.4)	80 (2.9)	141 (2.7)
Most common ^a SAEs that show treatment differences ^b by system organ class				
Neoplasms – benign, malignant and unspecified	0	6 (0.2)	4 (0.1)	10 (0.2)
Gastrointestinal disorders	4 (0.2)	5 (0.2)	7 (0.3)	12 (0.2)
Injury, poisoning and procedural complications	3 (0.2)	17 (0.7)	0	17 (0.3)
Most common ^c SAEs that show treatment differences ^b by preferred term				
Uterine leiomyoma	0	3 (0.1)	2 (0.1)	5 (0.1)
Lymphopenia	0	3 (0.1)	1 (<0.1)	4 (0.1)

SAE = serious adverse event.

^aReported in >1% of patients in any treatment group.

^bThe percentage of patients in one active treatment group is $\geq 2 \times$ the percentage of patients in the placebo group, or the percentage of patients in the placebo group is $\geq 2 \times$ the percentage of patients in the active treatment group.

^cReported in >0.5% of patients in any treatment group.

initiated chemotherapy, but died about three months after diagnosis.

The acute cardiopulmonary arrest was considered to be due to an exacerbation of pre-existing tuberculosis. A 21-year-old female in the 5.25 mg/kg group received a single treatment course of cladribine tablets (0.875 mg/kg). At approximately one week after her last dose of cladribine she developed pancytopenia after which she was permanently withdrawn from treatment. A second episode of pancytopenia occurred approximately two months after the end of cladribine treatment. A chest x-ray showed bilateral alveolar-interstitial infiltrates and a bone marrow biopsy performed six days later showed 'slight myelodysplasia'. At approximately five months after the last dose of cladribine tablets, the patient experienced a third episode of pancytopenia. A chest x-ray showed recurrent bilateral alveolar-interstitial lung infiltrates and a repeat bone marrow examination revealed an apparent myelodysplastic syndrome. The patient died from an acute cardiopulmonary arrest approximately six months after receiving a single 0.875 mg/kg treatment course of cladribine. The diagnosis of tuberculosis was obtained post-mortem, and the chronic pathologic nature of lesions in the liver and lungs, together with the temporal relationship between treatment and acute onset of symptoms,

suggested that the tuberculosis was long-standing and present prior to cladribine treatment. Cladribine therapy likely contributed to the worsening of the tuberculosis infection. The myelodysplasia-like condition was probably reactive bone marrow changes caused by the chronic tuberculosis infection and upon review by the DSMB (in particular, the hematologist/oncologist representative who reviewed the microscopy slides prepared from the patient's bone marrow aspirates) this was determined not to be a case of true myelodysplastic syndrome as there were no cytogenetic abnormalities and its presentation was not consistent with the natural history of myelodysplasia. In addition, according to the National Centre of Pharmacovigilance of Tunisia report, myelodysplasia did not seem to be associated with cladribine, given the low dosage taken by the patient (0.875 mg/kg) and the brief interval separating its onset and the start of therapy.

Events of special interest

Hematologic events

In the cladribine 3.5 mg/kg and 5.25 mg/kg groups, lymphopenia was reported as an AE in 21.6% and 31.5% of patients, respectively, compared with 1.8%

Table 7. Infections^a overview

Patients, <i>n</i> (%)	Placebo (<i>n</i> = 435)	Cladribine 3.5 mg/kg (<i>n</i> = 430)	Cladribine 5.25 mg/kg (<i>n</i> = 454)	Cladribine overall (<i>n</i> = 884)
Any infection, weeks 0–96	185 (42.5)	205 (47.7)	222 (48.9)	427 (48.3)
Mild infections ^b	145 (33.3)	159 (37.0)	166 (36.6)	325 (36.8)
Moderate infections ^b	102 (23.4)	116 (27.0)	118 (26.0)	234 (26.5)
Severe infections ^b	3 (0.7)	2 (0.5)	8 (1.8)	10 (1.1)
Any infection, weeks 0–48	149 (34.3)	165 (38.4)	167 (36.8)	332 (37.6)
Any infection, weeks 48–96	102 (23.4)	141 (32.8)	140 (30.8)	281 (31.8)
Events, <i>n</i> (%)	(<i>n</i> = 1,958)	(<i>n</i> = 2,514)	(<i>n</i> = 2,712)	(<i>n</i> = 5,226)
Any infection, weeks 0–96	500 (25.5)	550 (21.9)	571 (21.1)	1,121 (21.5)
Mild infections	330 (16.9)	354 (14.1)	358 (13.2)	712 (13.6)
Moderate infections	165 (8.4)	194 (7.7)	205 (7.6)	399 (7.6)
Severe infections	5 (0.3)	2 (0.1)	8 (0.3)	10 (0.2)
Any infection, weeks 0–48	295 (15.1)	315 (12.5)	305 (11.2)	620 (11.9)
Any infection, weeks 48–96	205 (10.5)	235 (9.3)	266 (9.8)	501 (9.6)

^aAEs within the Infections and infestations Medical Dictionary for Regulatory Activities (MedDRA) system organ class.

^bSome patients may have had mild, moderate and severe infections so may have been counted more than once.

of patients in the placebo group during the entire 96-week study. In addition, 'lymphocyte count decreased' was reported for another 39 patients, 13 (3.0%) in the 3.5 mg/kg and 26 (5.7%) in the 5.25 mg/kg (Table 4). All of these events can be considered as lymphopenia as there was no material difference between the events reported by the investigators as 'lymphopenia' and as 'lymphocyte count decreased.'

Five (0.6%) patients in the cladribine-treated groups (three in the 3.5 mg/kg group and two in the 5.25 mg/kg group) experienced 12 hematologic SAEs (four lymphopenia, three neutropenia, one leukopenia, one pancytopenia and three thrombocytopenia) versus no patients in the placebo group. One patient (who suffered the previously discussed fatal exacerbation of pre-existing tuberculosis) experienced six of the 12 events: two neutropenia, one pancytopenia and three thrombocytopenia events.

Infections

During the 96-week study, infections and infestations were reported in 42.5%, 47.7%, and 48.9% of patients in the placebo, cladribine 3.5 mg/kg and 5.25 mg/kg groups, respectively (Table 7). During weeks 0–48, infections occurred in 34.3%, 38.4%, and 36.8% of patients, respectively, compared to 23.4%, 32.8% and 30.8% of patients, respectively, during weeks 48–96 (Table 7). In the placebo and cladribine 3.5 mg/kg and 5.25 mg/kg treatment groups, 495 of 500 (99.0%), 548 of 550 (99.6%) and 563 of 571 (98.6%) infection events were rated by investigators as mild or moderate

(Table 7). Infections that occurred in greater than 1% of patients in any treatment group and showed two-fold treatment group differences are listed in Table 4.

Twenty (2.3%) patients treated with cladribine tablets developed 21 cases of herpes zoster (including one case of herpes zoster oticus or Ramsay-Hunt syndrome): eight patients in the 3.5 mg/kg group (1.9%; one patient during weeks 0–48 and seven patients during weeks 48–96) and 12 patients in the 5.25 mg/kg group (2.6%; seven patients during weeks 0–48 and five patients during weeks 48–96) (Table 4). One patient who was listed as having had two herpes zoster events had dates of infection onset separated by eight days and both events involved the same dermatome, raising suspicion about the distinct nature of the two events. There were no cases of herpes zoster in the placebo group. Of the 21 herpes zoster cases, 19 were assessed by investigators as mild or moderate. All 21 cases were dermatomal in nature and no case was disseminated. The case of herpes zoster oticus in the 5.25 mg/kg group was the only case associated with clinical sequelae; persistent, intermittent right-sided ear pain, which was reported to have stabilized by the end of the trial. The incidence of herpes zoster in patients treated with cladribine tablets was 13 cases per 1,000 patient-years. There were three cases of herpes varicella (one in each of the treatment groups) and all cases resolved without any complication. Herpes simplex infections (including oral herpes, genital herpes, herpes dermatitis and herpes ophthalmic) occurred in all three treatment groups; 10 (2.3%) patients in the placebo group developed 15 infections, 6 (1.4%) patients in the cladribine

3.5 mg/kg group developed 12 infections and 21 (4.6%) patients in the 5.25 mg/kg group developed 30 infections. Of the 57 herpes simplex infections, 56 were rated by investigators as mild or moderate.

SAE infections and infestations occurred in 1.6%, 2.3% and 2.9% of patients in the placebo, cladribine 3.5 mg/kg and 5.25 mg/kg groups, respectively. Three cases of herpes zoster were treated in hospital with antiviral medication and therefore met the definition for an SAE (one in the cladribine 3.5 mg/kg group and two in the 5.25 mg/kg group). One of these cases was rated as severe (the case of herpes zoster oticus) while the other two were rated as moderate. There was one case of exacerbation of a pre-existing, chronic tuberculosis infection, as discussed previously (see SAEs and deaths section). Pneumonia occurred with equal frequency across the groups (0.7%).

Neoplasms

AEs related to benign uterine leiomyomas were reported in one patient (0.2%) treated with placebo, five patients (1.2%) treated with cladribine 3.5 mg/kg, and four patients (0.9%) treated with cladribine 5.25 mg/kg (Table 4). Five cases met the definition for an SAE (three in the 3.5 mg/kg group and two in the 5.25 mg/kg group). Two of the five SAE cases presented with uterine bleeding, and the other three were discovered during unrelated gynecologic examinations. One of the patients had several known risk factors for uterine leiomyomas, including obesity and a contraceptive implant received four years prior to study entry. Another patient had an established history of uterine leiomyomas beginning two years prior to participation in the study. Three of these five patients underwent hysterectomy. All five cases were reported to have

resolved by the end of the study. The incidence of uterine leiomyomas in cladribine-exposed females during the study was 8.6 cases per 1,000 women-years.

Three cases of malignancy across different organ systems were reported during the study in patients treated with cladribine tablets (all in the cladribine 3.5 mg/kg group; a malignant melanoma, a pancreatic carcinoma and an ovarian carcinoma). Time from the first treatment course to diagnosis in these patients was: 14 months, 17 months and within 12 months, respectively (Table 8). The patient with ovarian carcinoma was lost to follow-up so the exact time from first treatment to diagnosis is unknown. There were no malignancies during the study in patients treated with placebo. The SIR for the three malignancies diagnosed during the study compared with the expected rate in a population matched for country, gender and age was 0.99 (95% confidence interval: 0.25, 2.70).

One patient treated with cladribine 5.25 mg/kg was diagnosed with choriocarcinoma approximately nine months following completion of the study (31 months after her first treatment course; Table 8). As a post-study event, this was not included in the calculation of the SIR. In addition, a cervical carcinoma in situ Stage 0 case (also known as cervical intraepithelial neoplasia Grade 3) was reported during the study in the cladribine 5.25 mg/kg group in a patient who had received four courses of cladribine tablets (total exposure 3.5 mg/kg). Time from first treatment course to diagnosis was ten months and relevant medical history included HPV16 positivity three years prior to diagnosis. This event was initially reported as a malignancy by the site investigator but was re-evaluated because cervical intraepithelial neoplasia Grade 3 is a cervical cancer precursor.¹¹ Given the nature of this neoplasm, incidence rates for cervical carcinoma in situ are not

Table 8. Malignancies

Age, yrs Gender	Total exposure	First treatment to diagnosis	Description and history
During study – cladribine 3.5 mg/kg group			
61 Female	6 courses, 3.5 mg/kg	17 months	Pancreatic carcinoma, liver metastases History of chronic gastroduodenitis, stomach diverticulum, gastric ulcer, cholelithiasis with cholecystectomy, hypertension, cardiac insufficiency, hyperlipoproteinemia, and asthma (treated with chronic steroids); non-smoker, no alcohol
48 Female	6 courses, 3.5 mg/kg	14 months	Melanoma stage IIA, T3a, N0 M0 History of hypertension
46 Female	4 courses, 1.75 mg/kg	<12 months	Ovarian carcinoma Unconfirmed (patient lost to follow-up); no relevant medical history
At post-study surveillance – cladribine 5.25 mg/kg group			
26 Female	6 courses, 5.25 mg/kg	31 months	Choriocarcinoma Diagnosed after therapeutic abortion ~9 months after study completion

provided in the *Cancer Incidence in Five Continents Vol. IX*⁹ and therefore the event was not included in the calculation of the SIR. As discussed in the section on SAEs and deaths, myelodysplastic syndrome was reported in the cladribine 5.25 mg/kg group in the patient who experienced an exacerbation of pre-existing tuberculosis. However, the tuberculosis was considered to be the underlying cause for the development of the myelodysplastic changes.

Vital signs and electrocardiograms

There was no appreciable difference, at baseline and over time, in vital sign and electrocardiogram assessments across treatment groups.

Laboratory abnormalities

All patients treated with cladribine tablets experienced reductions in their lymphocyte counts as expected based on the mechanism of action of cladribine. In the placebo, cladribine 3.5 mg/kg and 5.25 mg/kg groups, lymphocyte counts remained at Grade 0 (i.e. within normal limits) during the 96-week study in 83.2%, 10.2%, and 4.2% of patients, respectively. Grade 3 and 4 lymphopenias occurred in 0.5%, 25.6%, and 44.9% of patients in the placebo, cladribine 3.5 mg/kg and 5.25 mg/kg groups, respectively, during the study (Table 9). Sixteen patients treated with cladribine tablets developed Grade 4 lymphopenia. The majority (75%) of the cases of Grade 4 lymphopenia incidence were observed after dosing of patients already

experiencing Grade 3 lymphopenia. During weeks 0–48, Grade 3 and 4 lymphopenias developed in 0.2%, 11.4% and 33.5% of patients in the placebo, cladribine 3.5 mg/kg and 5.25 mg/kg groups, respectively, and during weeks 48–96, in 0.2%, 22.1% and 32.8% of patients, respectively.

Among a total of 314 patients in the cladribine tablets treatment groups who developed a Grade 3 or 4 lymphopenia at any time during the study, only 35 (11.1%) patients (10 treated with 3.5 mg/kg and 25 treated with 5.25 mg/kg) had persistent lymphopenia (i.e. had not returned to a lesser Grade 2 or Grade 1 lymphopenia or had not normalized their lymphocyte count at the final study evaluation). There were no cases of persistent Grade 4 lymphopenia. In 18 of 35 patients, the designation of persistent Grade 3 lymphopenia was the result of a Grade 3 lymphopenia first being detected at the last study visit (either at week 96 or at the time of early withdrawal from the study).

Grade 3 and 4 neutropenia occurred much less frequently, and with similar frequencies across treatment groups; 4.1%, 2.8%, and 4.2% of patients in the placebo, cladribine 3.5 and 5.25 mg/kg groups, respectively. Grade 3 leukopenia occurred in 0.5%, 1.4%, and 2.2% of patients in the placebo, cladribine 3.5 mg/kg and 5.25 mg/kg groups, respectively, and Grade 4 leukopenia occurred in 0.2% of patients in the cladribine 5.25 mg/kg group. Although no cases of Grade 3 or 4 thrombocytopenia were reported as a laboratory abnormality in the cladribine treatment groups, it should be noted that Grade 3 thrombocytopenias were recorded outside of the central laboratory in the

Table 9. Grade 3 and 4 laboratory abnormalities

Laboratory abnormality, n (%)	Placebo (n = 435)		Cladribine 3.5 mg/kg (n = 430)		Cladribine 5.25 mg/kg (n = 454)	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Hematologic						
Lymphocytes decreased	2 (0.5)	0	107 (24.9)	3 (0.7)	191 (42.1)	13 (2.9)
Neutrophils decreased	12 (2.8)	6 (1.4)	5 (1.2)	7 (1.6)	14 (3.1)	5 (1.1)
WBC decreased	2 (0.5)	0	6 (1.4)	0	10 (2.2)	1 (0.2)
Hemoglobin decreased	3 (0.7)	0	5 (1.2)	0	1 (0.2)	0
Platelet count decreased	1 (0.2)	0	0	0	0 ^a	0
Hepatobiliary						
Alkaline phosphatase increased	0	0	0	0	0	0
ALT increased	4 (0.9)	0	5 (1.2)	0	3 (0.7)	0
AST increased	1 (0.2)	0	2 (0.5)	0	1 (0.2)	0
Bilirubin increased	0	0	2 (0.5)	0	1 (0.2)	0
Renal						
Serum creatinine increased	0	0	0	1 (0.2)	0	0

ALT = alanine aminotransferase; AST = aspartate aminotransferase; WBC = white blood cell count.

^aNote: Grade 3 thrombocytopenias were recorded outside of the central laboratory in the patient who experienced an exacerbation of pre-existing tuberculosis.

patient who experienced an exacerbation of pre-existing tuberculosis. A Grade 3 reduction in hemoglobin occurred in 0.7%, 1.2% and 0.2% of patients in the placebo, cladribine 3.5 mg/kg and 5.25 mg/kg groups, respectively (Table 9).

The incidence of Grade 3 laboratory abnormalities related to hepatic function in the two cladribine tablets treatment groups was low (<2%) and comparable to that observed in the placebo group (Table 9). There were no patients who fulfilled the criteria for a Hy's Law case.¹² In terms of laboratory abnormalities related to renal function, one patient treated with cladribine 3.5 mg/kg experienced a Grade 4 elevation of serum creatinine at the week 9 blood test (Table 9). However, no AE was reported and the patient completed all six cycles of treatment with otherwise normal values for serum creatinine. There was no clear explanation for the Grade 4 measurement but it did not appear to be related to cladribine treatment.

Relationship between lymphocyte counts and herpes zoster

Of the 20 patients who developed herpes zoster infections, ten patients experienced Grade 3 or 4 lymphopenia at any time during the study. Thus, herpes zoster infections developed in ten of 314 (3.18%) patients treated with cladribine tablets who experienced Grade 3 or 4 lymphopenia at any time during the study and in ten of 570 (1.75%) patients treated with cladribine tablets that did not experience Grade 3 or 4 lymphopenia during the study. Serial lymphocyte measurements

showed that lymphocyte counts were within Grade 0, 1, 2, and 3 for three, three, eight, and six patients, respectively, at the approximate time of zoster infection. Thus, 70% of the patients who developed herpes zoster infections had normal lymphocyte counts or Grade 1–2 lymphopenia at the approximate time of infection.

Pregnancies

There were 24 pregnancies in 23 female study participants. In the placebo, cladribine 3.5 mg/kg and 5.25 mg/kg groups, the number of pregnancies was six, seven and 11, respectively (Table 10). Of the 24 pregnancies, six were conceived during treatment (i.e. the pregnancy occurred within a 28-day treatment cycle), 17 were conceived during the study when the patient was not receiving treatment and one was conceived six months after the patient had completed the study. With regard to outcomes, there were five normal term live births (three in the placebo group and two in the 5.25 mg/kg cladribine group), one ectopic pregnancy (in the cladribine 3.5 mg/kg group), 13 elective abortions (11 in the cladribine groups), one therapeutic abortion due to choriocarcinoma (in the cladribine 5.25 mg/kg group) and four miscarriages (three in the cladribine groups; Table 10). Both of the patients in the cladribine 5.25 mg/kg group who had normal term live births had received six courses of cladribine tablets, with conceptions occurring approximately two weeks and approximately 25 weeks after the sixth treatment course.

Table 10. Pregnancies in study participants^a

	Placebo	Cladribine 3.5 mg/kg	Cladribine 5.25 mg/kg	Total
Number of pregnancies	6	7	11	24
Number of patients	6	6	11	23
Treatment status at time of conception, n (%)				
During treatment ^b	3 ^d	1	2	6
Off treatment ^c	3	6	8	17
Post study	0	0	1	1
Pregnancy outcomes, n (%)				
Miscarriage	1	1	2	4
Elective abortion	2	5	6	13
Therapeutic abortion	0	0	1	1
Ectopic pregnancy	0	1	0	1
Normal term live birth	3	0	2	5

^aAn additional pregnancy, which resulted in a normal term live birth, occurred in the partner of a male study participant in the cladribine 5.25 mg/kg group; conception occurred approximately 6 months after he received his fourth course of treatment (his third course was missed).

^bDuring treatment = patient was within the 28-day treatment cycle.

^cOff treatment = patient had completed all study treatment or completed first four cycles but not started the last two cycles of treatment.

^dOne of these patients conceived after receiving 6 months of rescue therapy with interferon beta-1a.

There was one additional pregnancy in the partner of a male study participant. This patient was randomized to cladribine 5.25 mg/kg and his partner conceived approximately 30 weeks after his scheduled fourth treatment course. He did not receive his third course of cladribine tablets as he did not attend the week 9 study visit. The outcome of this pregnancy was a normal term live birth.

Four patients were unblinded by investigators when pregnancy was confirmed to facilitate decision-making about continuation of the pregnancy. Two were in the cladribine 5.25 mg/kg group, one had a spontaneous miscarriage and one had an elective abortion, and the other two were in the placebo group and had normal term live births.

Discussion

In this trial setting, approximately 90% of patients treated with cladribine tablets completed treatment. Treatment and study discontinuations due to AEs suggest that the 3.5 mg/kg regimen may be better tolerated than the 5.25 mg/kg regimen. These doses were chosen with the aim of exerting the maximal therapeutic effect while minimizing lymphopenia, and were based on the results from studies on parenteral cladribine in MS patients.^{3–6} In general, treatment discontinuations due to AEs were relatively few, although a greater proportion of patients withdrew prematurely from treatment due to AEs in the cladribine tablets groups compared with the placebo group. This may be partially explained by the protocol recommendations for recurrent or prolonged Grade 3 or 4 hematologic abnormalities (see Methods/management of hematologic abnormalities). After subtracting discontinuations due to lymphopenia and related AEs, the proportions of patients discontinuing treatment due to AEs in the cladribine tablets groups were closer to the proportions in the placebo group. In the placebo group, a greater proportion of patients withdrew from treatment due to perceived lack of efficacy/disease progression compared with the active treatment groups.

The incidence of most reported AEs was comparable across treatment groups; a notable exception was lymphopenia, which was anticipated based on the mechanism of action of cladribine and was the most commonly reported AE in the cladribine tablets groups. There was a possible dose-relationship for certain AEs, indicated by a higher incidence in the cladribine 5.25 mg/kg group as compared with the cladribine 3.5 mg/kg or placebo groups. In the case of lymphopenia and leukopenia, their incidence was also higher in the cladribine 3.5 mg/kg group versus the placebo group, whereas vertigo, tinnitus and hypesthesia occurred in similar proportions of patients in the

cladribine 3.5 mg/kg and placebo groups. In the 3.5 mg/kg group, the frequency of laboratory Grade 3 and 4 lymphopenia increased from 11.4% of patients during weeks 0–48 to 22.1% of patients during weeks 48–96, whereas in the 5.25 mg/kg group the frequencies remained similar across the two treatment periods (33.5% and 32.8%). Few cases of Grade 4 lymphopenia developed during the study, and 75% of those that did can be attributed to dosing during Grade 3 lymphopenia. The protocols for ongoing studies have been amended and incorporate additional procedural measures designed to prevent re-treatment in patients with a coincident Grade 3 lymphopenia. No increased risk of infection during weeks 48–96 versus weeks 0–48 was identified in any treatment group, despite the increased incidence of Grade 3 and 4 lymphopenia during weeks 48–96 in the cladribine 3.5 mg/kg group.

The overall incidence of infections and infestations as well as SAE infections and infestations was slightly higher in the cladribine tablets treatment groups versus placebo. However, approximately 99% of infections and infestations were considered as mild or moderate in severity across the three treatment groups. This may be partially explained by the targeted effect of cladribine on lymphocytes. While peripheral T and B cell populations are reduced by cladribine, cells of the innate immune system, which play an important role in fighting infections, are relatively spared. Moreover, B cells and natural killer cells recover progressively prior to the second 48-week treatment period and T cells persist at around one third to half of baseline levels.

Treatment with cladribine tablets was associated with an increased risk of developing herpes zoster. Twenty (2.3%) patients treated with cladribine tablets developed herpes zoster, while there were no cases in the placebo group. Notably, no case was disseminated. The incidence of herpes zoster in patients treated with cladribine tablets in the CLARITY study was 13 cases per 1,000 patient-years which compares with approximately four cases per 1,000 person-years found in the general population over the last two decades.^{13–16} When comparing the incidence in the MS population and in the general population, it should be noted that the incidence of herpes zoster is higher in women^{17,18} and in older individuals.¹⁹

The likely contribution of treatment with cladribine tablets to the exacerbation of pre-existing tuberculosis in one patient that subsequently died highlights the importance of screening patients for tuberculosis prior to treatment and annual re-treatment with cladribine tablets, a measure which has been implemented in all ongoing clinical trials of this drug.

There was a trend suggesting that patients who developed Grade 3 or 4 lymphopenia at any time during the study had an increased incidence of herpes

zoster compared with those not developing Grade 3 or 4 lymphopenia. However, analysis of serial lymphocyte counts and the timing of herpes zoster infection did not reveal a clear association between the degree of lymphopenia and the occurrence of infection, as 70% of patients who developed herpes zoster had normal lymphocyte counts ($n=3$) or Grade 1–2 lymphopenia ($n=11$) at the approximate time of infection. However, it may be that it is not overall lymphopenia, but rather a loss of viral-specific T cells that is relevant for the risk of herpes zoster infection.²⁰ Additional immunophenotypic analyses may reveal a clearer association between the effects of cladribine tablets treatment on the immune system and herpes zoster infection.

Three malignancies occurred in the cladribine tablets treatment groups during the 96-week study and one was reported during post-study surveillance. There were no malignancies in the placebo group. The SIR does not suggest an increased risk of malignancy in patients treated with cladribine tablets over 96 weeks compared to the reference population. It is therefore not possible to estimate risk with precision at this time and continued vigilance will be necessary. AEs related to benign uterine leiomyomas occurred in all three treatment groups during the study with a greater incidence in the cladribine tablets groups. Since uterine leiomyomas are very common and many are asymptomatic, it is not known how many leiomyomas represented *de novo* cases and how many were pre-existing conditions that became clinically manifest during the study. At least two patients (one with a SAE leiomyoma and one with a non-SAE leiomyoma) had a history of uterine leiomyomas prior to participation in the study. Despite the increased incidence among patients treated with cladribine tablets versus placebo, the observed incidence of uterine leiomyomas in cladribine-exposed females within the CLARITY study (8.6 cases per 1,000 women-years) does not seem to be in excess of the population incidence of 12.8 per 1,000 women-years.²¹ The incidence of uterine leiomyoma increases with age in premenopausal women.²¹ The ongoing 96-week extension of the CLARITY study will provide further information on the therapeutic profile of cladribine tablets exposure for up to 4 years.²² In addition, a patient registry has been established to assess longer term safety outcomes (up to 8 years) in patients who participated in the cladribine tablets clinical development program.²³

Twenty-five pregnancies were conceived during the CLARITY study despite the requirement that patients should use contraception to avoid pregnancy. This reinforces the need for highly effective contraception (i.e. methods with a Pearl index²⁴ [the expected number of pregnancies per 100 women-years of exposure] of $\leq 1\%$) during cladribine treatment. Three normal term infants

were born to patients or partners of patients who had completed 3–6 courses of cladribine tablets approximately 2–30 weeks prior to conception. These results are encouraging, although the effects of cladribine tablets on human reproduction and development remain unknown.

Conclusion

The observed safety results from the CLARITY study support the potential for cladribine tablets as an MS therapy. However, treatment with cladribine tablets was associated with an increased risk of herpes zoster. Continued monitoring of the safety profile, in particular events of special interest including infections and malignancies, will be essential to fully define the risks associated with this therapy; this will be explored further in ongoing studies.

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Conflict of interest statement

Professor Cook has received honoraria for lectures from Merck Serono and Bayer Healthcare and consultation fees from Sanofi-Aventis, Bayer Healthcare, Merck Serono and Actinobac Scientific Inc. He serves on scientific advisory boards for Bayer Healthcare, Merck Serono and Actinobac Scientific Inc. He has received research grants for the BEYOND and BECOME studies from Bayer Healthcare and the CLARITY and CLARITY EXTENSION studies from Merck Serono.

Professor Vermersch has received consulting fees for speaker and advisory board activities from Merck Serono, Bayer Schering and Teva-Aventis, Biogen Idec, and Novartis; lecture fees from Merck Serono, Biogen Idec, Bayer Schering, and Novartis; and grant support from Biogen Idec, Merck Serono, and Teva-Aventis.

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References

- Leist TP and Vermersch P. The potential role for cladribine in the treatment of multiple sclerosis: clinical experience and development of an oral tablet formulation. *Curr Med Res Opin* 2007; 23: 2667–2676.
- Cohen BA. Evolving views of MS pathogenesis. *Int J MS Care* 2007; 9: 4–10.
- Beutler E, Sipe JC, Romine JS, Koziol JA, McMillan R and Zyroff J. The treatment of chronic progressive multiple sclerosis with cladribine. *Proc Natl Acad Sci USA* 1996; 93: 1716–1720.
- Rice GP, Filippi M and Comi G. Cladribine and progressive MS: clinical and MRI outcomes of a multicenter controlled trial. Cladribine MRI Study Group. *Neurology* 2000; 54: 1145–1155.
- Romine JS, Sipe JC, Koziol JA, Zyroff J and Beutler E. A double-blind, placebo-controlled, randomized trial of cladribine in relapsing-remitting multiple sclerosis. *Proc Assoc Am Physicians* 1999; 111: 35–44.
- Sipe JC, Romine JS, Koziol JA, McMillan R, Zyroff J and Beutler E. Cladribine in treatment of chronic progressive multiple sclerosis. *Lancet* 1994; 344: 9–13.
- Giovannoni G, Comi G, Cook S, Rammohan K, Rieckmann P, Sorensen PS, et al. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. *N Engl J Med* 2010; 362: 416–426.
- International Agency for Research on Cancer (IARC). *Statistical methods in cancer research volume 2: The design and analysis of cohort studies*, 82nd edn. Lyon, France: International Agency for Research on Cancer (IARC) Scientific Publications, 1987, pp.49–65.
- International Agency for Research on Cancer (IARC). Cancer Incidence in Five Continents, Vol IX, No.160. http://www-dep.iarc.fr/CI5_IX_frame.htm (accessed 9 June 2009).
- GLOBOCAN. The GLOBOCAN 2002 database. <http://www-dep.iarc.fr/globocan/database.htm> (accessed April 2009).
- ACOG. American College of Obstetricians and Gynecologists Practice Bulletin No.99: Management of Abnormal Cervical Cytology and Histology. *Obstet Gynecol* 2008; 112: 1419–1444.
- US Food and Drug Administration. Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation. 29 July 2009. <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064993.htm> (accessed 2 September 2010).
- Chapman RS, Cross KW and Fleming DM. The incidence of shingles and its implications for vaccination policy. *Vaccine* 2003; 21: 2541–2547.
- Jumaan AO, Yu O, Jackson LA, Bohlke K, Galil K and Seward JF. Incidence of herpes zoster, before and after varicella-vaccination-associated decreases in the incidence of varicella, 1992–2002. *J Infect Dis* 2005; 191: 2002–2007.
- Yawn BP, Saddier P, Wollan PC, St Sauver JL, Kurland MJ and Sy LS. A population-based study of the incidence and complication rates of herpes zoster before zoster vaccine introduction. *Mayo Clin Proc* 2007; 82: 1341–1349.
- Chidiac C, Bruxelles J, Daures JP, Hoang-Xuan T, Morel P, Leplege A, et al. Characteristics of patients with herpes zoster on presentation to practitioners in France. *Clin Infect Dis* 2001; 33: 62–69.
- Fleming DM, Cross KW, Cobb WA and Chapman RS. Gender difference in the incidence of shingles. *Epidemiol Infect* 2004; 132: 1–5.
- Opstelten W, van Essen GA, Schellevis F, Verheij TJ and Moons KG. Gender as an independent risk factor for herpes zoster: a population-based prospective study. *Ann Epidemiol* 2006; 16: 692–695.
- Gnann JW and Whitley RJ. Clinical practice. Herpes zoster. *N Engl J Med* 2002; 347: 340–346.
- Gershon AA, Gershon MD, Breuer J, Levin MJ, Oaklander AL and Griffiths PD. Advances in the understanding of the pathogenesis and epidemiology of herpes zoster. *J Clin Virol* 2010; 48: S2–S7.
- Marshall LM, Spiegelman D, Barbieri RL, Goldman MB, Manson JE, Colditz GA, et al. Variation in the incidence of uterine leiomyoma among premenopausal women by age and race. *Obstet Gynecol* 1997; 90: 967–973.

22. Viglietta V, Greenberg S, Mikol D, Weiner J, Alteri E, Chang P, et al. Clinical development plan for cladribine tablets, an oral immunomodulator, for the treatment of multiple sclerosis. (Annual Congress of European Committee for Treatment and Research in Multiple Sclerosis, Dusseldorf, Germany, 9–12 September 2009). (P439). *Mult Scler* 2009; 15: S126–S127.
23. Miret M, Perez-Gutthann S, Gutierrez L, Viglietta V, Musch B and Greenberg S. Evaluation of the long-term safety of cladribine tablets: design of a prospective observational 8-year safety registry. (Annual Congress of European Committee for Treatment and Research in Multiple Sclerosis, Dusseldorf, Germany, 9–12 September 2009). (P788). *Mult Scler* 2009; 15: S239.
24. Pearl R. Factors in human fertility and their statistical evaluation. *Lancet* 1933; 222: 607–611.