ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
Release Date: 01/10/2014

ClinicalTrials.gov ID: NCT00213135

Study Identification

Unique Protocol ID:	25643
Brief Title:	A Safety and Efficacy Study of Oral Cladribine in Subjects With Relapsing-remitting Multiple Sclerosis (RRMS) (CLARITY)
Official Title:	A Phase III, Randomized, Double-blind, Three-arm, Placebo-controlled, Multi-center Study to Evaluate the Safety and Efficacy of Oral Cladribine in Subjects With Relapsing-remitting Multiple Sclerosis (RRMS)
Secondary IDs:	

Study Status

Record Verification:	January 2014
Overall Status:	Completed
Study Start:	April 2005
Primary Completion:	November 2008 [Actual]
Study Completion:	November 2008 [Actual]

Sponsor/Collaborators

Sponsor:	EMD Serono
Responsible Party:	Sponsor
Collaborators:	

Oversight

FDA Regulated?:	Yes
Applicable Trial?:	Section 801 Clinical Trial? Yes

	Delayed Posting? No
IND/IDE Protocol?:	Yes
IND/IDE Information:	Grantor: CBER IND/IDE Number: 74634 Serial Number: 000 Has Expanded Access? No
Review Board:	Approval Status: Approved Approval Number: 04/12/2006 Board Name: Coast Independent Review Board, LLC Board Affiliation: Independent Phone: 949-218-9969 Email: info@coastirb.com
Data Monitoring?:	
Plan to Share Data?:	
Oversight Authorities:	United States: Food and Drug Administration

Study Description

Brief Summary:	The purpose of the study is to determine if cladribine tablets are a safe and effective treatment for relapsing-remitting multiple sclerosis (RRMS).
Detailed Description:	This is a randomized, double-blind, three-arm, placebo-controlled, multi-center study. The study includes a pre-study evaluation period (up to 28 days prior to the start of treatment); an initial treatment period from Week 1 to 48; and a re-treatment period during Week 49 to 96. During the initial treatment period (Week 1 to 48), eligible subjects are equally randomized by a central randomization system to receive either a) cladribine at a low dose (0.875 milligram per kilogram per course [mg/kg/course] for two courses plus placebo for two courses); b) cladribine at a high dose (0.875 mg/kg/course for four courses); or c) placebo (four courses). During the re-treatment period (Weeks 49 to 96), subjects received either a) cladribine at a low dose (0.875 mg/kg/course for two courses); or b) placebo (two courses). For all randomized subjects, there is a rescue option of treatment with Rebif® (interferon beta-1a 44 microgram (mcg) given subcutaneously three times a week), if the subject experienced more than one qualifying relapse, and/or experienced a sustained increase in their EDSS score of greater than or equal to (>=) 1 point, or >=1.5 points if baseline EDSS score is 0, (over a period of three months or greater), during a calendar year beginning at Week 24. To maintain the blind, there is a treating physician who view clinical laboratory results and assess adverse events and safety information, and an independent blinded evaluating physician who will perform neurological exams. A central neuroradiology center, also blinded to treatment, will assess magnetic resonance imaging (MRI) evaluations.

Conditions

Conditions: Multiple Sclerosis, Relapsing-Remitting

Keywords:

Study Design

Study Type: Interventional

Primary Purpose: Treatment

Study Phase: Phase 3

Intervention Model: Parallel Assignment

Number of Arms: 3

Masking: Double Blind (Subject, Caregiver, Investigator)

Allocation: Randomized

Endpoint Classification: Safety/Efficacy Study

Enrollment: 1326 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Cladribine 5.25 mg/kg	Drug: Cladribine 5.25 mg/kg Cladribine tablet will be administered as cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4 or 5 consecutive days of 28-day period at Week 1, 5, 9, 13, 48, and 52 resulting in total cladribine dose of 5.25 mg/kg during the treatment period of 96 weeks.
Experimental: Cladribine 3.5 mg/kg	Drug: Cladribine 3.5 mg/kg Cladribine tablet will be administered as cumulative dose of 0.875 mg/kg over a course of 4 or 5 consecutive days of 28-day period at Weeks 1, 5, 48, and 52 and placebo matched to cladribine tablet will be administered at Week 9 and 13 resulting in total cladribine dose of 3.5 mg/kg during the treatment period of 96 weeks.
Placebo Comparator: Placebo	Placebo Placebo matched to cladribine tablet will be administered over a course of 4 or 5 consecutive days of 28-day period at Weeks 1, 5, 9, 13, 48 and 52 during the treatment period of 96 weeks.

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age: 18 Years

Maximum Age: 65 Years

Gender: Both

Accepts Healthy Volunteers?: No

Criteria: Inclusion Criteria:

- Male or female, between 18 and 65 years of age (inclusive, at time of informed consent)
- Has definite MS according to the McDonald criteria
- Has relapsing-remitting disease with 1 or more relapses within 12 months prior to Study Day 1
- Must have been clinically stable and not has a relapse within 28 days prior to Study Day 1
- Has MRI consistent with MS at the pre-study evaluation according to the Fazekas criteria
- Has a EDSS score from 0 to 5.5, inclusive
- Weighed between 40-120 kilogram (kg), inclusive
- If female, she must:
    a. be post-menopausal or surgically sterilized; or
    b. uses a hormonal contraceptive, intra uterine device, diaphragm with spermicide, or condom with spermicide, for the duration of the study; and
    c. be neither pregnant nor breast-feeding
- If male, he must be willing to use contraception to avoid pregnancies
- Be willing and able to comply with study procedures for the duration of the study
- Voluntarily provides written informed consent, and for United states of America (USA) sites only, a subject authorization under Health Insurance Portability and Accountability Act (HIPAA)

Exclusion Criteria:

- Has secondary progressive MS (SPMS) or primary progressive MS (PPMS)
- Prior use of disease modifying drugs (DMDs) within the last 3 months, or 2 or more prior treatment failures with DMDs on the basis of efficacy
- Has significant leukopenia (white blood cell count less than 0.5 times the lower limit of normal of the central laboratory) within 28 days prior to Study Day 1
- Has received cladribine, mitoxantrone, total lymphoid irradiation, myelosuppressive therapy, campath-1h, cyclophosphamide, azathioprine, methotrexate or natalizumab
- Has received oral or systemic corticosteroids or adrenocorticotropic hormone within 28 days prior to Study Day 1
- Has compromised immune function or infection
- Has received oral or systemic corticosteroids or adrenocorticotropic hormone within 28 days prior to Study Day 1

- Has received cytokine-based therapy, intravenous immunoglobulin therapy, or plasmapheresis within 3 months prior to Study Day 1
- Has platelet and absolute neutrophil counts below the lower limit of normal range within 28 days prior to Study Day 1
- Has prior or current history of malignancy
- Has a history of persistent anemia, leukopenia, neutropenia, or thrombocytopenia after immunosuppressive therapy
- Has systemic disease that, in the opinion of the Investigator, might interfere with subject safety, compliance or evaluation of the condition under Study (for example, insulin-dependent diabetes, Lyme disease, clinically significant cardiac, hepatic, or renal disease, Human Immunodeficiency Virus, or Human T-Cell Lymphotrophic Virus Type-1)
- Has a psychiatric disorder that, in the opinion of the Investigator, was unstable or would preclude safe participation in the study
- Has allergy or hypersensitivity to gadolinium, to cladribine or any of its excipients
- Has used any investigational drug or experimental procedure within 6 months prior to Study Day 1

Contacts/Locations

Study Officials: Steven J. Greenberg, M.D.
Study Director
EMD Serono, Inc.

Locations:

References

Citations: [Study Results] Giovannoni G, Comi G, Cook S, Rammohan K, Rieckmann P, Soelberg Sørensen P, Vermersch P, Chang P, Hamlett A, Musch B, Greenberg SJ; CLARITY Study Group. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. N Engl J Med. 2010 Feb 4;362(5):416-26. doi: 10.1056/NEJMoa0902533. Epub 2010 Jan 20. PubMed 20089960

Links:

Study Data/Documents:

Study Results

Participant Flow

Reporting Groups

	Description
Cladribine 5.25 mg/kg	Cladribine tablet administered as cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4 or 5 consecutive days of 28-day period at Week 1, 5, 9, 13, 48, and 52 resulting in total cladribine dose of 5.25 mg/kg during the treatment period of 96 weeks.
Cladribine 3.5 mg/kg	Cladribine tablet administered as cumulative dose of 0.875 mg/kg over a course of 4 or 5 consecutive days of 28-day period at Week 1, 5, 48, and 52 and placebo matched to cladribine tablet was administered at Week 9 and 13 resulting in total cladribine dose of 3.5 mg/kg during the treatment period of 96 weeks.
Placebo	Placebo matched to cladribine tablet administered over a course of 4 or 5 consecutive days of 28-day period at Week 1, 5, 9, 13, 48 and 52 during the treatment period of 96 weeks.

Overall Study

	Cladribine 5.25 mg/kg	Cladribine 3.5 mg/kg	Placebo
Started	456	433	437
Completed	406	398	380
Not Completed	50	35	57
Adverse Event	9	5	5
Lost to Follow-up	11	8	4
Protocol Violation	4	4	10
Death	1	1	2
Disease progression	4	5	21
Unspecified	21	12	15

Baseline Characteristics

Reporting Groups

	Description
Cladribine 5.25 mg/kg	Cladribine tablet administered as cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4 or 5 consecutive days of 28-day period at Week 1, 5, 9, 13, 48, and 52 resulting in total cladribine dose of 5.25 mg/kg during the treatment period of 96 weeks.

	Description
Cladribine 3.5 mg/kg	Cladribine tablet administered as cumulative dose of 0.875 mg/kg over a course of 4 or 5 consecutive days of 28-day period at Week 1, 5, 48, and 52 and placebo matched to cladribine tablet was administered at Week 9 and 13 resulting in total cladribine dose of 3.5 mg/kg during the treatment period of 96 weeks.
Placebo	Placebo matched to cladribine tablet administered over a course of 4 or 5 consecutive days of 28-day period at Week 1, 5, 9, 13, 48 and 52 during the treatment period of 96 weeks.

Baseline Measures

	Cladribine 5.25 mg/kg	Cladribine 3.5 mg/kg	Placebo	Total
Number of Participants	456	433	437	1326
Age, Continuous [units: years] Mean (Standard Deviation)	39.1 (9.9)	37.9 (10.3)	38.7 (9.9)	38.6 (10.0)
Gender, Male/Female [units: participants]				
Female	312	298	288	898
Male	144	135	149	428

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Annualized Qualifying Relapse Rate
Measure Description	A qualifying relapse was defined as an increase of 2 points in at least one functional system of the expanded disability status scale (EDSS) or an increase of 1 point in at least two functional systems (excluding changes in bowel or bladder function or cognition) in the absence of fever, lasting for at least 24 hours and to have been preceded by at least 30 days of clinical stability or improvement. Expanded disability status scale (EDSS) assesses disability in 8 functional systems. An overall score ranging from 0 (normal) to 10 (death due to multiple sclerosis [MS]) was calculated. The annualized relapse rate for each treatment group was calculated as the total number of confirmed relapses divided by the total number of days on study multiplied by 365.25.
Time Frame	Week 96
Safety Issue?	No

Analysis Population Description

The intention-to-treat (ITT) population included all participants who were randomized in the study.

Reporting Groups

	Description
Cladribine 5.25 mg/kg	Cladribine tablet administered as cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4 or 5 consecutive days of 28-day period at Week 1, 5, 9, 13, 48, and 52 resulting in total cladribine dose of 5.25 mg/kg during the treatment period of 96 weeks.
Cladribine 3.5 mg/kg	Cladribine tablet administered as cumulative dose of 0.875 mg/kg over a course of 4 or 5 consecutive days of 28-day period at Week 1, 5, 48, and 52 and placebo matched to cladribine tablet was administered at Week 9 and 13 resulting in total cladribine dose of 3.5 mg/kg during the treatment period of 96 weeks.
Placebo	Placebo matched to cladribine tablet administered over a course of 4 or 5 consecutive days of 28-day period at Week 1, 5, 9, 13, 48 and 52 during the treatment period of 96 weeks.

Measured Values

	Cladribine 5.25 mg/kg	Cladribine 3.5 mg/kg	Placebo
Number of Participants Analyzed	456	433	437
Annualized Qualifying Relapse Rate [units: relapses per year] Number (95% Confidence Interval)	0.15 (0.12 to 0.17)	0.14 (0.12 to 0.17)	0.33 (0.29 to 0.38)

Statistical Analysis 1 for Annualized Qualifying Relapse Rate

Statistical Analysis Overview	Comparison Groups	Cladribine 5.25 mg/kg, Placebo
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.001
	Comments	[Not specified]
	Method	Other [Wald Chi-square test]
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Other [Relative Risk]
	Estimated Value	0.43
	Confidence Interval	(2-Sided) 95% 0.35 to 0.54

	Parameter Dispersion	Type: Standard Error of the mean Value: 0.11
	Estimation Comments	[Not specified]

Statistical Analysis 2 for Annualized Qualifying Relapse Rate

Statistical Analysis Overview	Comparison Groups	Cladribine 3.5 mg/kg, Placebo
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.001
	Comments	[Not specified]
	Method	Other [Wald Chi-square test]
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Other [Relative Risk]
	Estimated Value	0.43
	Confidence Interval	(2-Sided) 95% 0.34 to 0.54
	Parameter Dispersion	Type: Standard Error of the mean Value: 0.12
	Estimation Comments	[Not specified]

2. Secondary Outcome Measure:

Measure Title	Percentage of Relapse-free Participants
Measure Description	A qualifying relapse was defined as an increase of 2 points in at least one functional system of the EDSS or an increase of 1 point in at least two functional systems (excluding changes in bowel or bladder function or cognition) in the absence of fever, lasting for at least 24 hours and to have been preceded by at least 30 days of clinical stability or improvement. Expanded disability status scale (EDSS) assesses disability in 8 functional systems. An overall score ranging from 0 (normal) to 10 (death due to MS) was calculated.
Time Frame	Week 96
Safety Issue?	No

Analysis Population Description

The ITT population included all participants who were randomized in the study.

Reporting Groups

	Description
Cladribine 5.25 mg/kg	Cladribine tablet administered as cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4 or 5 consecutive days of 28-day period at Week 1, 5, 9, 13, 48, and 52 resulting in total cladribine dose of 5.25 mg/kg during the treatment period of 96 weeks.
Cladribine 3.5 mg/kg	Cladribine tablet administered as cumulative dose of 0.875 mg/kg over a course of 4 or 5 consecutive days of 28-day period at Week 1, 5, 48, and 52 and placebo matched to cladribine tablet was administered at Week 9 and 13 resulting in total cladribine dose of 3.5 mg/kg during the treatment period of 96 weeks.
Placebo	Placebo matched to cladribine tablet administered over a course of 4 or 5 consecutive days of 28-day period at Week 1, 5, 9, 13, 48 and 52 during the treatment period of 96 weeks.

Measured Values

	Cladribine 5.25 mg/kg	Cladribine 3.5 mg/kg	Placebo
Number of Participants Analyzed	456	433	437
Percentage of Relapse-free Participants [units: percentage of participants]	78.9	79.7	60.9

3. Secondary Outcome Measure:

Measure Title	Time to Disability Progression
Measure Description	Time to disability progression was defined as the time to a sustained increase in EDSS score of at least 1 point if baseline EDSS score between 0.5 and 4.5 inclusively, or at least 1.5 points if the baseline EDSS score was 0, or at least 0.5 point if the baseline EDSS score was at least 5, over a period of at least three months. Expanded disability status scale (EDSS) assesses disability in 8 functional systems. An overall score ranging from 0 (normal) to 10 (death due to MS) was calculated. Tenth Percentile of time to sustained increase in EDSS score was reported using Kaplan-Meier survival curve.
Time Frame	Baseline up to Week 96
Safety Issue?	No

Analysis Population Description

The ITT population included all participants who were randomized in the study.

Reporting Groups

	Description
Cladribine 5.25 mg/kg	Cladribine tablet administered as cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4 or 5 consecutive days of 28-day period at Week 1, 5, 9, 13, 48, and 52 resulting in total cladribine dose of 5.25 mg/kg during the treatment period of 96 weeks.
Cladribine 3.5 mg/kg	Cladribine tablet administered as cumulative dose of 0.875 mg/kg over a course of 4 or 5 consecutive days of 28-day period at Week 1, 5, 48, and 52 and placebo matched to cladribine tablet was administered at Week 9 and 13 resulting in total cladribine dose of 3.5 mg/kg during the treatment period of 96 weeks.
Placebo	Placebo matched to cladribine tablet administered over a course of 4 or 5 consecutive days of 28-day period at Week 1, 5, 9, 13, 48 and 52 during the treatment period of 96 weeks.

Measured Values

	Cladribine 5.25 mg/kg	Cladribine 3.5 mg/kg	Placebo
Number of Participants Analyzed	456	433	437
Time to Disability Progression [units: months]	13.6	13.6	10.8

4. Secondary Outcome Measure:

Measure Title	Mean Number of Combined Unique (CU) Lesions, Active Time Constant 2 (T2) Lesions, and Active Time Constant 1 (T1) Gadolinium-Enhanced (Gd+) Lesions Per Participant Per Scan
Measure Description	Mean Number of CU lesions, active T2 lesions, and active T1 Gd+ lesions were measured by using magnetic resonance imaging (MRI) scans.
Time Frame	Week 96
Safety Issue?	No

Analysis Population Description

The ITT population included all participants who were randomized in the study.

Reporting Groups

	Description
Cladribine 5.25 mg/kg	Cladribine tablet administered as cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4 or 5 consecutive days of 28-day period at Week 1, 5, 9, 13, 48, and 52 resulting in total cladribine dose of 5.25 mg/kg during the treatment period of 96 weeks.

	Description
Cladribine 3.5 mg/kg	Cladribine tablet administered as cumulative dose of 0.875 mg/kg over a course of 4 or 5 consecutive days of 28-day period at Week 1, 5, 48, and 52 and placebo matched to cladribine tablet was administered at Week 9 and 13 resulting in total cladribine dose of 3.5 mg/kg during the treatment period of 96 weeks.
Placebo	Placebo matched to cladribine tablet administered over a course of 4 or 5 consecutive days of 28-day period at Week 1, 5, 9, 13, 48 and 52 during the treatment period of 96 weeks.

Measured Values

	Cladribine 5.25 mg/kg	Cladribine 3.5 mg/kg	Placebo
Number of Participants Analyzed	456	433	437
Mean Number of Combined Unique (CU) Lesions, Active Time Constant 2 (T2) Lesions, and Active Time Constant 1 (T1) Gadolinium-Enhanced (Gd+) Lesions Per Participant Per Scan [units: lesions] Least Squares Mean (Standard Error)			
CU lesions	0.38 (0.08)	0.43 (0.08)	1.72 (0.08)
Active T1 Gd+ lesions	0.11 (0.05)	0.12 (0.05)	0.91 (0.05)
Active T2 lesions	0.33 (0.06)	0.38 (0.07)	1.43 (0.06)

Reported Adverse Events

Time Frame	Baseline up to Week 96
Additional Description	Safety population included all the randomized participants who received at least one dose of stud medication with follow-up safety data

Reporting Groups

	Description
Cladribine 5.25 mg/kg	Cladribine tablet administered as cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4 or 5 consecutive days of 28-day period at Week 1, 5, 9, 13, 48, and 52 resulting in total cladribine dose of 5.25 mg/kg during the treatment period of 96 weeks.

	Description
Cladribine 3.5 mg/kg	Cladribine tablet administered as cumulative dose of 0.875 mg/kg over a course of 4 or 5 consecutive days of 28-day period at Week 1, 5, 48, and 52 and placebo matched to cladribine tablet was administered at Week 9 and 13 resulting in total cladribine dose of 3.5 mg/kg during the treatment period of 96 weeks.
Placebo	Placebo matched to cladribine tablet administered over a course of 4 or 5 consecutive days of 28-day period at Week 1, 5, 9, 13, 48 and 52 during the treatment period of 96 weeks.

Serious Adverse Events

	Cladribine 5.25 mg/kg	Cladribine 3.5 mg/kg	Placebo
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	41/454 (9.03%)	36/430 (8.37%)	28/435 (6.44%)
Blood and lymphatic system disorders			
Leukopenia [A] *	0/454 (0%)	1/430 (0.23%)	0/435 (0%)
Lymphopenia [A] *	1/454 (0.22%)	3/430 (0.7%)	0/435 (0%)
Neutropenia [A] *	1/454 (0.22%)	1/430 (0.23%)	0/435 (0%)
Pancytopenia [A] *	1/454 (0.22%)	0/430 (0%)	0/435 (0%)
Thrombocytopenia [A] *	1/454 (0.22%)	0/430 (0%)	0/435 (0%)
Cardiac disorders			
Acute myocardial infarction [A] *	0/454 (0%)	0/430 (0%)	1/435 (0.23%)
Angina pectoris [A] *	0/454 (0%)	0/430 (0%)	1/435 (0.23%)
Arrhythmia [A] *	0/454 (0%)	0/430 (0%)	1/435 (0.23%)
Bundle branch block left [A] *	0/454 (0%)	0/430 (0%)	1/435 (0.23%)
Cardiac hypertrophy [A] *	0/454 (0%)	0/430 (0%)	1/435 (0.23%)
Cardio-respiratory arrest [A] *	1/454 (0.22%)	0/430 (0%)	0/435 (0%)
Cardiomyopathy [A] *	0/454 (0%)	0/430 (0%)	1/435 (0.23%)
Myocardial infarction [A] *	0/454 (0%)	1/430 (0.23%)	0/435 (0%)
Prinzmetal angina [A] *	1/454 (0.22%)	0/430 (0%)	0/435 (0%)

	Cladribine 5.25 mg/kg	Cladribine 3.5 mg/kg	Placebo
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Endocrine disorders			
Hyperthyroidism [A] *	1/454 (0.22%)	0/430 (0%)	0/435 (0%)
Eye disorders			
Eyelid ptosis [A] *	0/454 (0%)	0/430 (0%)	1/435 (0.23%)
Gastrointestinal disorders			
Abdominal pain upper [A] *	1/454 (0.22%)	0/430 (0%)	0/435 (0%)
Colitis ulcerative [A] *	0/454 (0%)	1/430 (0.23%)	0/435 (0%)
Food poisoning [A] *	0/454 (0%)	0/430 (0%)	1/435 (0.23%)
Gastric ulcer [A] *	0/454 (0%)	1/430 (0.23%)	0/435 (0%)
Gastritis erosive [A] *	1/454 (0.22%)	0/430 (0%)	0/435 (0%)
Gastrointestinal motility disorder [A] *	0/454 (0%)	0/430 (0%)	1/435 (0.23%)
Haemorrhoids [A] *	1/454 (0.22%)	0/430 (0%)	0/435 (0%)
Ileus [A] *	1/454 (0.22%)	0/430 (0%)	0/435 (0%)
Inguinal hernia [A] *	0/454 (0%)	1/430 (0.23%)	0/435 (0%)
Nausea [A] *	1/454 (0.22%)	0/430 (0%)	0/435 (0%)
Pancreatitis acute [A] *	0/454 (0%)	0/430 (0%)	1/435 (0.23%)
Pancreatitis relapsing [A] *	0/454 (0%)	0/430 (0%)	1/435 (0.23%)
Peritonitis [A] *	0/454 (0%)	1/430 (0.23%)	0/435 (0%)
Small intestinal perforation [A] *	0/454 (0%)	1/430 (0.23%)	0/435 (0%)
Toothache [A] *	1/454 (0.22%)	0/430 (0%)	0/435 (0%)
Vomiting [A] *	1/454 (0.22%)	0/430 (0%)	0/435 (0%)
General disorders			
Asthenia [A] *	0/454 (0%)	1/430 (0.23%)	0/435 (0%)

	Cladribine 5.25 mg/kg	Cladribine 3.5 mg/kg	Placebo
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Chest pain [A] *	1/454 (0.22%)	0/430 (0%)	1/435 (0.23%)
Drowning [A] *	1/454 (0.22%)	0/430 (0%)	0/435 (0%)
Non-cardiac chest pain [A] *	1/454 (0.22%)	0/430 (0%)	0/435 (0%)
Oedema peripheral [A] *	1/454 (0.22%)	0/430 (0%)	0/435 (0%)
Pyrexia [A] *	1/454 (0.22%)	0/430 (0%)	1/435 (0.23%)
Hepatobiliary disorders			
Cholecystitis [A] *	1/454 (0.22%)	0/430 (0%)	0/435 (0%)
Cholecystitis acute [A] *	0/454 (0%)	1/430 (0.23%)	0/435 (0%)
Cholelithiasis [A] *	2/454 (0.44%)	1/430 (0.23%)	0/435 (0%)
Hepatic cyst [A] *	0/454 (0%)	0/430 (0%)	1/435 (0.23%)
Hepatitis [A] *	1/454 (0.22%)	0/430 (0%)	0/435 (0%)
Hepatitis acute [A] *	1/454 (0.22%)	0/430 (0%)	0/435 (0%)
Hepatitis toxic [A] *	0/454 (0%)	1/430 (0.23%)	1/435 (0.23%)
Hepatosplenomegaly [A] *	1/454 (0.22%)	0/430 (0%)	0/435 (0%)
Liver disorder [A] *	0/454 (0%)	0/430 (0%)	1/435 (0.23%)
Immune system disorders			
Hypersensitivity [A] *	2/454 (0.44%)	0/430 (0%)	0/435 (0%)
Infections and infestations			
Actinomycosis [A] *	1/454 (0.22%)	0/430 (0%)	0/435 (0%)
Adnexitis [A] *	2/454 (0.44%)	0/430 (0%)	0/435 (0%)
Appendicitis [A] *	0/454 (0%)	0/430 (0%)	2/435 (0.46%)
Chronic sinusitis [A] *	0/454 (0%)	0/430 (0%)	1/435 (0.23%)

	Cladribine 5.25 mg/kg	Cladribine 3.5 mg/kg	Placebo
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Cystitis [A] *	1/454 (0.22%)	0/430 (0%)	0/435 (0%)
Endometritis [A] *	1/454 (0.22%)	0/430 (0%)	0/435 (0%)
Hepatitis C [A] *	0/454 (0%)	0/430 (0%)	1/435 (0.23%)
Herpes zoster [A] *	0/454 (0%)	1/430 (0.23%)	0/435 (0%)
Herpes zoster infection neurological [A] *	1/454 (0.22%)	0/430 (0%)	0/435 (0%)
Herpes zoster oticus [A] *	1/454 (0.22%)	0/430 (0%)	0/435 (0%)
Influenza [A] *	0/454 (0%)	1/430 (0.23%)	0/435 (0%)
Lung abscess [A] *	1/454 (0.22%)	0/430 (0%)	0/435 (0%)
Myocarditis bacterial [A] *	0/454 (0%)	0/430 (0%)	1/435 (0.23%)
Orchitis [A] *	1/454 (0.22%)	0/430 (0%)	0/435 (0%)
Pneumonia [A] *	3/454 (0.66%)	3/430 (0.7%)	3/435 (0.69%)
Pyelonephritis [A] *	0/454 (0%)	2/430 (0.47%)	0/435 (0%)
Respiratory tract infection [A] *	1/454 (0.22%)	0/430 (0%)	0/435 (0%)
Salpingo-oophoritis [A] *	0/454 (0%)	1/430 (0.23%)	0/435 (0%)
Subcutaneous abscess [A] *	0/454 (0%)	1/430 (0.23%)	0/435 (0%)
Tuberculosis [A] *	1/454 (0.22%)	0/430 (0%)	0/435 (0%)
Urinary tract infection [A] *	1/454 (0.22%)	1/430 (0.23%)	0/435 (0%)
Injury, poisoning and procedural complications			
Ankle fracture [A] *	0/454 (0%)	2/430 (0.47%)	0/435 (0%)
Concussion [A] *	0/454 (0%)	1/430 (0.23%)	0/435 (0%)
Facial bones fracture [A] *	0/454 (0%)	1/430 (0.23%)	0/435 (0%)
Fall [A] *	0/454 (0%)	2/430 (0.47%)	0/435 (0%)

	Cladribine 5.25 mg/kg	Cladribine 3.5 mg/kg	Placebo
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Femoral neck fracture [A] *	0/454 (0%)	1/430 (0.23%)	0/435 (0%)
Femur fracture [A] *	0/454 (0%)	0/430 (0%)	1/435 (0.23%)
Joint dislocation [A] *	0/454 (0%)	1/430 (0.23%)	0/435 (0%)
Lumbar vertebral fracture [A] *	0/454 (0%)	1/430 (0.23%)	0/435 (0%)
Overdose [A] *	0/454 (0%)	1/430 (0.23%)	0/435 (0%)
Pneumothorax traumatic [A] *	0/454 (0%)	0/430 (0%)	1/435 (0.23%)
Postoperative ileus [A] *	0/454 (0%)	1/430 (0.23%)	0/435 (0%)
Radius fracture [A] *	0/454 (0%)	1/430 (0.23%)	0/435 (0%)
Rib fracture [A] *	0/454 (0%)	0/430 (0%)	1/435 (0.23%)
Subdural haematoma [A] *	0/454 (0%)	1/430 (0.23%)	0/435 (0%)
Tibia fracture [A] *	0/454 (0%)	1/430 (0.23%)	0/435 (0%)
Upper limb fracture [A] *	0/454 (0%)	1/430 (0.23%)	0/435 (0%)
Wound dehiscence [A] *	0/454 (0%)	1/430 (0.23%)	0/435 (0%)
Metabolism and nutrition disorders			
Cachexia [A] *	1/454 (0.22%)	0/430 (0%)	0/435 (0%)
Hyperglycaemia [A] *	0/454 (0%)	0/430 (0%)	1/435 (0.23%)
Hypoproteinaemia [A] *	1/454 (0.22%)	0/430 (0%)	0/435 (0%)
Musculoskeletal and connective tissue disorders			
Arthritis [A] *	1/454 (0.22%)	0/430 (0%)	0/435 (0%)
Bone pain [A] *	1/454 (0.22%)	0/430 (0%)	0/435 (0%)
Intervertebral disc protrusion [A] *	0/454 (0%)	1/430 (0.23%)	0/435 (0%)
Myalgia [A] *	0/454 (0%)	1/430 (0.23%)	0/435 (0%)

	Cladribine 5.25 mg/kg	Cladribine 3.5 mg/kg	Placebo
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Osteitis [A] *	1/454 (0.22%)	0/430 (0%)	0/435 (0%)
Pain in extremity [A] *	1/454 (0.22%)	0/430 (0%)	1/435 (0.23%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cervix carcinoma stage 0 [A] *	1/454 (0.22%)	0/430 (0%)	0/435 (0%)
Malignant melanoma [A] *	0/454 (0%)	1/430 (0.23%)	0/435 (0%)
Myelodysplastic syndrome [A] *	1/454 (0.22%)	0/430 (0%)	0/435 (0%)
Ovarian cancer [A] *	0/454 (0%)	1/430 (0.23%)	0/435 (0%)
Pancreatic carcinoma metastatic [A] *	0/454 (0%)	1/430 (0.23%)	0/435 (0%)
Uterine leiomyoma [A] *	2/454 (0.44%)	3/430 (0.7%)	0/435 (0%)
Nervous system disorders			
Altered state of consciousness [A] *	0/454 (0%)	1/430 (0.23%)	0/435 (0%)
Convulsion [A] *	0/454 (0%)	1/430 (0.23%)	0/435 (0%)
Epilepsy [A] *	1/454 (0.22%)	0/430 (0%)	0/435 (0%)
Facial spasm [A] *	0/454 (0%)	0/430 (0%)	1/435 (0.23%)
Haemorrhagic stroke [A] *	0/454 (0%)	0/430 (0%)	1/435 (0.23%)
Syncope [A] *	1/454 (0.22%)	0/430 (0%)	0/435 (0%)
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous [A] *	1/454 (0.22%)	1/430 (0.23%)	1/435 (0.23%)
Ectopic pregnancy [A] *	0/454 (0%)	1/430 (0.23%)	0/435 (0%)
Pregnancy [A] *	1/454 (0.22%)	1/430 (0.23%)	1/435 (0.23%)
Psychiatric disorders			
Completed suicide [A] *	0/454 (0%)	0/430 (0%)	1/435 (0.23%)
Delirium [A] *	1/454 (0.22%)	0/430 (0%)	0/435 (0%)

	Cladribine 5.25 mg/kg	Cladribine 3.5 mg/kg	Placebo
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Depression [A] *	0/454 (0%)	0/430 (0%)	1/435 (0.23%)
Intentional self-injury [A] *	0/454 (0%)	0/430 (0%)	1/435 (0.23%)
Mental disorder [A] *	0/454 (0%)	1/430 (0.23%)	0/435 (0%)
Panic attack [A] *	0/454 (0%)	0/430 (0%)	1/435 (0.23%)
Schizophrenia, paranoid type [A] *	1/454 (0.22%)	0/430 (0%)	0/435 (0%)
Suicide attempt [A] *	2/454 (0.44%)	0/430 (0%)	0/435 (0%)
Renal and urinary disorders			
Calculus ureteric [A] *	0/454 (0%)	0/430 (0%)	1/435 (0.23%)
Nephrolithiasis [A] *	0/454 (0%)	1/430 (0.23%)	0/435 (0%)
Nephrosclerosis [A] *	0/454 (0%)	0/430 (0%)	1/435 (0.23%)
Renal artery stenosis [A] *	1/454 (0.22%)	0/430 (0%)	0/435 (0%)
Renal colic [A] *	0/454 (0%)	1/430 (0.23%)	0/435 (0%)
Renal failure chronic [A] *	0/454 (0%)	1/430 (0.23%)	0/435 (0%)
Reproductive system and breast disorders			
Breast dysplasia [A] *	0/454 (0%)	0/430 (0%)	1/435 (0.23%)
Menorrhagia [A] *	1/454 (0.22%)	0/430 (0%)	0/435 (0%)
Metrorrhagia [A] *	1/454 (0.22%)	0/430 (0%)	0/435 (0%)
Ovarian cyst [A] *	1/454 (0.22%)	0/430 (0%)	0/435 (0%)
Uterine haemorrhage [A] *	0/454 (0%)	1/430 (0.23%)	0/435 (0%)
Respiratory, thoracic and mediastinal disorders			
Asthma [A] *	1/454 (0.22%)	0/430 (0%)	0/435 (0%)
Dyspnoea [A] *	2/454 (0.44%)	0/430 (0%)	1/435 (0.23%)

	Cladribine 5.25 mg/kg	Cladribine 3.5 mg/kg	Placebo
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Lung infiltration [A] *	1/454 (0.22%)	0/430 (0%)	0/435 (0%)
Pulmonary embolism [A] *	1/454 (0.22%)	0/430 (0%)	1/435 (0.23%)
Pulmonary oedema [A] *	0/454 (0%)	0/430 (0%)	1/435 (0.23%)
Skin and subcutaneous tissue disorders			
Hidradenitis [A] *	1/454 (0.22%)	0/430 (0%)	0/435 (0%)
Lichen sclerosus [A] *	0/454 (0%)	1/430 (0.23%)	0/435 (0%)
Purpura [A] *	1/454 (0.22%)	0/430 (0%)	0/435 (0%)
Rash generalised [A] *	1/454 (0.22%)	0/430 (0%)	0/435 (0%)
Skin reaction [A] *	1/454 (0.22%)	0/430 (0%)	0/435 (0%)
Vascular disorders			
Arterial disorder [A] *	0/454 (0%)	0/430 (0%)	1/435 (0.23%)
Deep vein thrombosis [A] *	1/454 (0.22%)	0/430 (0%)	0/435 (0%)
Hypertension [A] *	1/454 (0.22%)	0/430 (0%)	0/435 (0%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA (11.0)

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	Cladribine 5.25 mg/kg	Cladribine 3.5 mg/kg	Placebo
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	324/454 (71.37%)	286/430 (66.51%)	242/435 (55.63%)
Blood and lymphatic system disorders			
Leukopenia [A] *	39/454 (8.59%)	23/430 (5.35%)	3/435 (0.69%)
Lymphopenia [A] *	142/454 (31.28%)	92/430 (21.4%)	8/435 (1.84%)
Ear and labyrinth disorders			

	Cladribine 5.25 mg/kg	Cladribine 3.5 mg/kg	Placebo
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Vertigo [A] *	23/454 (5.07%)	14/430 (3.26%)	11/435 (2.53%)
Gastrointestinal disorders			
Diarrhoea [A] *	31/454 (6.83%)	30/430 (6.98%)	29/435 (6.67%)
Nausea [A] *	49/454 (10.79%)	43/430 (10%)	39/435 (8.97%)
General disorders			
Fatigue [A] *	27/454 (5.95%)	20/430 (4.65%)	26/435 (5.98%)
Influenza like illness [A] *	27/454 (5.95%)	34/430 (7.91%)	31/435 (7.13%)
Infections and infestations			
Influenza [A] *	34/454 (7.49%)	27/430 (6.28%)	27/435 (6.21%)
Nasopharyngitis [A] *	58/454 (12.78%)	62/430 (14.42%)	56/435 (12.87%)
Upper respiratory tract infection [A] *	52/454 (11.45%)	54/430 (12.56%)	42/435 (9.66%)
Urinary tract infection [A] *	32/454 (7.05%)	23/430 (5.35%)	39/435 (8.97%)
Investigations			
Lymphocyte count decreased [A] *	26/454 (5.73%)	13/430 (3.02%)	0/435 (0%)
Musculoskeletal and connective tissue disorders			
Arthralgia [A] *	23/454 (5.07%)	27/430 (6.28%)	21/435 (4.83%)
Back pain [A] *	39/454 (8.59%)	34/430 (7.91%)	28/435 (6.44%)
Pain in extremity [A] *	24/454 (5.29%)	16/430 (3.72%)	20/435 (4.6%)
Nervous system disorders			
Headache [A] *	94/454 (20.7%)	104/430 (24.19%)	75/435 (17.24%)
Psychiatric disorders			
Depression [A] *	25/454 (5.51%)	18/430 (4.19%)	13/435 (2.99%)
Insomnia [A] *	14/454 (3.08%)	25/430 (5.81%)	17/435 (3.91%)

	Cladribine 5.25 mg/kg	Cladribine 3.5 mg/kg	Placebo
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain [A] *	24/454 (5.29%)	19/430 (4.42%)	25/435 (5.75%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA (11.0)

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

Results Point of Contact:

Name/Official Title: Merck KGaA Communication Center
Organization: Merck Serono, a division of Merck KGaA
Phone: +49-6151-72-5200
Email: service@merckgroup.com