Clinical trial results:
Prospective observational long-term safety registry of Multiple Sclerosis patients who have participated in cladribine clinical studies (PREMIERE)

Summary

EudraCT number	2009-017978-21
Trial protocol	DE FI LT AT GR CZ GB EE LV BE SE PT DK ES IT PL BG
Global end of trial date	25 October 2018

Results information

Result version number	v1 (current)
This version publication date	09 November 2019
First version publication date	09 November 2019

Trial information

Trial identification

Sponsor protocol code	EMR700568-012

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01013350
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck KGaA, Darmstadt, Germany
Sponsor organisation address	Frankfurter Strasse 250,, Darmstadt, Germany, 64293
Public contact	Communication Centre, Merck KGaA, Darmstadt, Germany, +49 6151725200, service@merckgroup.com
Scientific contact	Communication Centre, Merck KGaA, Darmstadt, Germany, +49 6151725200, service@merckgroup.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 October 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 October 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main purpose of the PREMIERE registry was to collect long-term safety data on oral cladribine in subjects with Multiple sclerosis and to estimate the frequency of serious adverse drug reactions (SADRs) over a period of time, extending beyond oral cladribine exposure, in a population of subjects who have been exposed to oral cladribine.

Protection of trial subjects:

Subject protection was ensured by following high medical and ethical standards in accordance with the principles laid down in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and applicable regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 November 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 6
Country: Number of subjects enrolled	Australia: 7
Country: Number of subjects enrolled	Austria: 4
Country: Number of subjects enrolled	Belgium: 23
Country: Number of subjects enrolled	Bosnia and Herzegovina: 3
Country: Number of subjects enrolled	Bulgaria: 103
Country: Number of subjects enrolled	Canada: 8
Country: Number of subjects enrolled	Czech Republic: 45
Country: Number of subjects enrolled	Denmark: 14
Country: Number of subjects enrolled	Estonia: 28
Country: Number of subjects enrolled	Finland: 15
Country: Number of subjects enrolled	France: 38
Country: Number of subjects enrolled	Georgia: 10
Country: Number of subjects enrolled	Greece: 2
Country: Number of subjects enrolled	India: 3
Country: Number of subjects enrolled	Italy: 93
Country: Number of subjects enrolled	Korea, Republic of: 8
Country: Number of subjects enrolled	Latvia: 16
Country: Number of subjects enrolled	Lebanon: 39

Country: Number of subjects enrolled	Lithuania: 4
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Norway: 4
Country: Number of subjects enrolled	Poland: 50
Country: Number of subjects enrolled	Portugal: 12
Country: Number of subjects enrolled	Romania: 19
Country: Number of subjects enrolled	Russian Federation: 331
Country: Number of subjects enrolled	Saudi Arabia: 2
Country: Number of subjects enrolled	Serbia: 32
Country: Number of subjects enrolled	Singapore: 3
Country: Number of subjects enrolled	Spain: 25
Country: Number of subjects enrolled	Sweden: 5
Country: Number of subjects enrolled	Switzerland: 4
Country: Number of subjects enrolled	Taiwan: 3
Country: Number of subjects enrolled	Thailand: 1
Country: Number of subjects enrolled	Tunisia: 32
Country: Number of subjects enrolled	Turkey: 2
Country: Number of subjects enrolled	Ukraine: 48
Country: Number of subjects enrolled	United Kingdom: 29
Country: Number of subjects enrolled	United States: 76
Worldwide total number of subjects	1148
EEA total number of subjects	530

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	1138
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Study enrolled subjects from previous clinical trials (NCT00213135, NCT00436826, NCT00641537, NCT00938366 and NCT00725985) and were exposed either to placebo matched to cladribine or cladribine itself. 13 enrolled subjects from NCT00938366 were excluded from safety analysis as the dose was relatively lower compared with other studies.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Never Exposed to Cladribine

Arm description:

All subjects who received placebo matched to cladribine in previously conducted clinical trials (NCT Number: NCT00213135, NCT00436826 , NCT00641537 and NCT00725985).

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received placebo matched to cladribine in previously conducted clinical trials.

Arm title	Exposed to Cladribine

Arm description:

All subjects who received cladribine in previously conducted clinical trials (NCT Number: NCT00213135, NCT00436826 , NCT00641537 and NCT00725985).

Arm type	Experimental
Investigational medicinal product name	Cladribine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received cladribine in previously conducted clinical trials.

Number of subjects in period 1	Never Exposed to Cladribine	Exposed to Cladribine
Started	198	950
Safety Analysis Set	198	950
Completed	160	761
Not completed	38	189
Physician decision	4	20
Consent withdrawn by subject	15	36
Adverse event, non-fatal	-	1
Death	3	5
Participant entered interventional study	-	8
Unspecified	1	25
Lost to follow-up	15	94

Baseline characteristics

Reporting groups	
Reporting group title	Never Exposed to Cladribine
Reporting group description:	
All subjects who received placebo matched to cladribine in previously conducted clinical trials (NCT Number: NCT00213135, NCT00436826 , NCT00641537 and NCT00725985).	
Reporting group title	Exposed to Cladribine
Reporting group description:	
All subjects who received cladribine in previously conducted clinical trials (NCT Number: NCT00213135, NCT00436826 , NCT00641537 and NCT00725985).	

Reporting group values	Never Exposed to Cladribine	Exposed to Cladribine	Total
Number of subjects	198	950	1148
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	37.4	40.6	
standard deviation	± 10.2	± 10.8	-
Sex: Female, Male Units: Subjects			
Female	141	632	773
Male	57	318	375
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	0	1
Asian	5	13	18
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	7	7
White	190	925	1115
More than one race	0	0	0
Unknown or Not Reported	2	5	7

End points

End points reporting groups

Reporting group title	Never Exposed to Cladribine

Reporting group description:

All subjects who received placebo matched to cladribine in previously conducted clinical trials (NCT Number: NCT00213135, NCT00436826 , NCT00641537 and NCT00725985).

Reporting group title	Exposed to Cladribine

Reporting group description:

All subjects who received cladribine in previously conducted clinical trials (NCT Number: NCT00213135, NCT00436826 , NCT00641537 and NCT00725985).

Primary: Number of Subjects With Serious Adverse Drug Reactions (SADRs)

End point title	Number of Subjects With Serious Adverse Drug Reactions (SADRs)[1]

End point description:

SADR is an adverse drug reaction that fulfils at least one of the seriousness criterion; results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, is otherwise considered as medically important. An adverse drug reaction (ADR) is a response to a medicinal product which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the restoration, correction, or modification or physiological functions. Number of subjects with SADRs were reported. Safety analysis set included all subjects in the current study who either received placebo matched to cladribine or cladribine in previously conducted clinical trials (NCT Number: NCT00213135, NCT00436826 , NCT00641537 and NCT00725985).

End point type	Primary

End point timeframe:

up to 3251 days

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analysed for this endpoint.

End point values	Never Exposed to Cladribine	Exposed to Cladribine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	198	950		
Units: subjects	1	14		

Statistical analyses

No statistical analyses for this end point

Primary: Time to Resolution of Lymphopenia, Among Registry Subjects With Persistent Lymphopenia

End point title	Time to Resolution of Lymphopenia, Among Registry Subjects With Persistent Lymphopenia[2][3]

End point description:

Persistent lymphopenia was defined as Grade 3 (less than [<] 500-200 per millimeter [mm] ^3 or < 0.5–0.2 multiply [*]10^9 per Liter) or Grade 4 (< 200/mm^3 or < 0.2*10^9 per Liter) lymphopenia as defined by the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The resolution is

the achievement of a CTCAE Grade 1 (< lower limit of normal [LLN] to 800 per mm^3 or < LLN to 0.8*10^9 per Liter) or Grade 0 (< 910 per mm^3) lymphocyte count. Time to resolution was reported. Lymphocyte Population included subjects from safety analysis set who had persistent lymphopenia. Persistent Lymphopenia was reported only in Cladribine group, hence results are presented only for "Exposed to Cladribine" arm. Here, "number of subjects analyzed" signified subjects with resolved lymphopenia.

End point type	Primary

End point timeframe:

up to 3251 days

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analysed for this endpoint.

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Lymphopenia was reported only in Cladribine group, hence results are reported only for "Exposed to Cladribine" arm.

End point values	Exposed to Cladribine			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: months				
arithmetic mean (standard deviation)	30.22 (± 17.78)			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Adverse Events (AEs) in the "Blood and Lymphatic System Disorders" System Organ Class (SOC) and in the "Neoplasms Benign, Malignant, and Unspecified" SOC

End point title	Number of Subjects With Adverse Events (AEs) in the "Blood and Lymphatic System Disorders" System Organ Class (SOC) and in the "Neoplasms Benign, Malignant, and Unspecified" SOC[4]

End point description:

An Adverse event (AE) was defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study drug or worsening of pre-existing medical condition, whether or not related to study drug. Safety analysis set included all subjects in the current study who either received placebo matched to cladribine or cladribine in previously conducted clinical trials (NCT Number: NCT00213135, NCT00436826 , NCT00641537 and NCT00725985).

End point type	Primary

End point timeframe:

up to 3251 days

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analysed for this endpoint.

End point values	Never Exposed to Cladribine	Exposed to Cladribine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	198	950		
Units: subjects				
Blood and Lymphatic System Disorders SOC	18	92		
Neoplasms Benign, Malignant, and Unspecified SOC	4	25		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Pregnancy Outcomes

End point title	Number of Subjects with Pregnancy Outcomes

End point description:

Pregnancies occurred among female subjects exposed to cladribine were identified by a subject-reported positive pregnancy test and at least a 2-week delay in menses, or a subject-reported pregnancy diagnosed by a physician. Pregnancy outcomes were Live birth, Induced abortion (Termination), Spontaneous loss (Miscarriage) (< 22 weeks), Foetal death (stillbirth) (>=22 weeks), Ectopic pregnancy, Congenital malformations and others (unknown). Number of subjects as per pregnancy outcome category were reported. Safety analysis set included all subjects in the current study who either received placebo matched to cladribine or cladribine in previously conducted clinical trials (NCT Number: NCT00213135, NCT00436826 , NCT00641537 and NCT00725985). Here, number of subjects analysed signifies number of subjects with pregnancies.

End point type	Secondary

End point timeframe:

up to 3251 days

End point values	Never Exposed to Cladribine	Exposed to Cladribine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	57		
Units: subjects				
Live Birth	23	39		
Induced Abortion (Termination)	3	3		
Spontaneous Loss (Miscarriage)	2	3		
Foetal Death (Still birth)	0	1		
Ectopic Pregnancy	0	1		
Congenital Malformations	0	0		
Unknown	6	10		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: up to 3251 days	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups	
Reporting group title	Exposed to Cladribine
Reporting group description: All subjects who received cladribine in previously conducted clinical trials (NCT Number: NCT00213135, NCT00436826 , NCT00641537 and NCT00725985).	
Reporting group title	Never Exposed to Cladribine
Reporting group description: All subjects who received placebo matched to cladribine in previously conducted clinical trials (NCT Number: NCT00213135, NCT00436826 , NCT00641537 and NCT00725985).	

Serious adverse events	Exposed to Cladribine	Never Exposed to Cladribine	
Total subjects affected by serious adverse events			
subjects affected / exposed	63 / 950 (6.63%)	10 / 198 (5.05%)	
number of deaths (all causes)	5	3	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer stage II			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervix carcinoma			

subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Cervix carcinoma stage 0			
subjects affected / exposed	0 / 950 (0.00%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer stage 0			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to lung			
subjects affected / exposed	2 / 950 (0.21%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nonkeratinising carcinoma of nasopharynx			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papillary thyroid cancer			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polycythaemia vera			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal adenoma			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal cancer			

subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid adenoma			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal adenocarcinoma			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Ovarian germ cell teratoma benign			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Thrombophlebitis			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	0 / 950 (0.00%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stem cell transplant			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal			

conditions			
Abortion			
subjects affected / exposed	0 / 950 (0.00%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abortion missed			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abortion spontaneous			
subjects affected / exposed	2 / 950 (0.21%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abortion threatened			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foetal death			
subjects affected / exposed	2 / 950 (0.21%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foetal distress syndrome			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Premature separation of placenta			
subjects affected / exposed	0 / 950 (0.00%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Accidental death			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Non-cardiac chest pain			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Neonatal anoxia			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jealous delusion			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Brain herniation			

subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haemorrhage			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Dandy-Walker syndrome			
subjects affected / exposed	0 / 950 (0.00%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	0 / 950 (0.00%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Coronary artery insufficiency			
subjects affected / exposed	0 / 950 (0.00%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Myocardial infarction			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ataxia			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain oedema			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebellar syndrome			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparaesthesia			
subjects affected / exposed	0 / 950 (0.00%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Monoparesis			

subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple sclerosis			
subjects affected / exposed	1 / 950 (0.11%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Multiple sclerosis relapse			
subjects affected / exposed	8 / 950 (0.84%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 8	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Optic neuritis			
subjects affected / exposed	1 / 950 (0.11%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Relapsing-remitting multiple sclerosis			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Immune thrombocytopenic purpura			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenic purpura			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			

Vertigo			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo positional			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 950 (0.00%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal melanosis			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			

subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary incontinence			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Goitre			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid mass			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 950 (0.21%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc degeneration			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Intervertebral disc protrusion			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondylolisthesis			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Anal abscess			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 950 (0.00%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningoencephalitis herpetic			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pneumonia			

subjects affected / exposed	2 / 950 (0.21%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth infection			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 950 (0.00%)	1 / 198 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 950 (0.11%)	0 / 198 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Exposed to Cladribine	Never Exposed to Cladribine	
Total subjects affected by non-serious adverse events subjects affected / exposed	124 / 950 (13.05%)	26 / 198 (13.13%)	
Nervous system disorders Multiple sclerosis relapse subjects affected / exposed occurrences (all)	48 / 950 (5.05%) 48	11 / 198 (5.56%) 11	
Blood and lymphatic system disorders Lymphopenia subjects affected / exposed occurrences (all)	76 / 950 (8.00%) 76	15 / 198 (7.58%) 15	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 July 2012	Prospective collection of AEs in the 'Blood and Lymphatic System Disorders' and 'Neoplasms Benign, Malignant, and Unspecified' System Organ Classes (SOCs) and MS-related SAEs were started.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported