ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
Release Date: 08/04/2013

ClinicalTrials.gov ID: NCT00436826

Study Identification

Unique Protocol ID:	26593
Brief Title:	A Phase 2 Study of Cladribine Add-on to Interferon-beta (IFN-beta) Therapy in Multiple Sclerosis (MS) Subjects With Active Disease (ONWARD)
Official Title:	A Phase II, Multicenter, Randomized, Double Blind, Placebo Controlled, Safety, Tolerability and Efficacy Study of Add-on Cladribine Tablet Therapy With Interferon-beta (IFN-β) Treatment in Multiple Sclerosis Subjects With Active Disease
Secondary IDs:	2006-003366-33 [EudraCT Number]

Study Status

Record Verification:	August 2013
Overall Status:	Completed
Study Start:	November 2006
Primary Completion:	September 2011 [Actual]
Study Completion:	March 2012 [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: CDER IND/IDE Number: 74634; 5371 Serial Number: 023 Has Expanded Access? No
Review Board:	Approval Status: Approved Approval Number: 10/10/2006 Board Name: COAST IRB Board Affiliation: COAST IRB Phone: 949-218-9969 Email: DMcDaniel@coastirb.com
Data Monitoring?:	
Plan to Share Data?:	
Oversight Authorities:	United States: Food and Drug Administration

Study Description

Brief Summary: The goal of this study is to evaluate the safety, tolerability and effectiveness of oral cladribine when taken in combination with Interferon-beta (IFN-beta) therapy for the treatment of multiple sclerosis (MS).

This study will randomize around 200 subjects from approximately 50 sites located world-wide, who have experienced at least one relapse while taking IFN-beta therapy within 48 weeks prior to Screening, irrespective of disability progression. Secondary progressive multiple sclerosis (SPMS) subjects, who are still experiencing relapses, and subjects who have received disease modifying drugs (DMDs), other than IFN-beta therapy, during their MS treatment history, but are currently on IFN-beta therapy and have experienced active MS symptoms (at least 1 relapse) during the 48 weeks prior to Screening, may also be enrolled.

Subjects will be randomized in a 2:1 fashion to receive up to 4 cycles of oral cladribine or matching placebo in combination with IFN-beta therapy. Subjects who complete the double-blind portion of the study will be invited to participate in an open-label extension phase of matching study design. Total participation is 96 weeks in double blind period, and up to 48 weeks in open label extension phase.

Detailed Description:

Conditions

Conditions:	Multiple Sclerosis
Keywords:	Multiple Sclerosis Relapsing forms

Interferon-beta therapy

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 2
Intervention Model:	Parallel Assignment
Number of Arms:	2
Masking:	Double Blind (Subject, Investigator, Outcomes Assessor)
Allocation:	Randomized
Endpoint Classification:	Safety/Efficacy Study
Enrollment:	214 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Cladribine 3.5 mg/kg, IFN-beta	Drug: Cladribine Subjects will receive cladribine tablets orally as cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total cladribine dose of 3.5 mg/kg during the double blind (DB) period of 96 weeks. Subjects who will complete the DB period will to enter in open label (OL) extension period, if they meet the eligibility criteria they will be given total cladribine dose of 3.5 mg/kg over 48 weeks. Drug: Interferon-beta (IFN-beta) Subjects will receive IFN-beta therapy (Rebif® new formulation [RNF] 44 microgram [mcg] three times a week, subcutaneously; Avonex® 30 mcg every week, intramuscularly; or Betaseron® 250 mcg every other day, subcutaneously) during both DB period of 96 weeks and OL extension period of 48 weeks. Other Names: • Avonex® • Betaseron® • RNF
Placebo Comparator: Placebo, IFN-beta	Drug: Placebo

Arms	Assigned Interventions
	Subjects will receive matching placebo tablets orally as cumulative dose of 0.875 mg/kg over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total matching placebo dose of 3.5 mg/kg during the DB period of 96 weeks. Drug: Interferon-beta (IFN-beta) Subjects will receive IFN-beta therapy (Rebif® new formulation [RNF] 44 microgram [mcg] three times a week, subcutaneously; Avonex® 30 mcg every week, intramuscularly; or Betaseron® 250 mcg every other day, subcutaneously) during both DB period of 96 weeks and OL extension period of 48 weeks. Other Names: • Avonex® • Betaseron® • RNF

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age: 18 Years

Maximum Age: 65 Years

Gender: Both

Accepts Healthy Volunteers?: No

Criteria: Inclusion Criteria:

- Be male or female, 18 to 65 years of age (inclusive)
- Weigh between 40 to 120 kilogram (kg), (inclusive)
- Have definite MS, as confirmed by the revised McDonald criteria 2005, and have relapsing forms of MS, such as relapsing-remitting multiple sclerosis (RRMS) or SPMS with superimposed relapses
- Have experienced at least one relapse within 48 weeks prior to Screening, while receiving IFN-beta treatments (Rebif® 44mcg three times a week, subcutaneously; Avonex®30 mcg every week, intramuscular; or Betaseron® 250 mcg every other day, subcutaneously)
- Have a minimum time on IFN-beta therapy of 48-consecutive weeks prior to Screening. Subjects who switched from one IFN-beta therapy to another in the 48 weeks preceding Screening may be entered into the study if they have been on a stable regimen of their current IFN-beta therapy for a minimum of 3 months prior to Screening
- Be clinically stable (other than MS relapse) during the 28 days preceding Screening

- The following hematological parameters must be normal (as defined below, inclusively) within 28 days of first dosing of blinded study medication at study day 1 (SD 1)
    - Hemoglobin=11.6 to 16.2 gram per deciliter (g/dL)
    - Leukocytes (total white blood cells [WBC])=4.1 to 12.3*10^3 per microliter (/UL)
    - Absolute lymphocytes count (ALC)= 1.02 to 3.36*10^3/UL
    - Absolute neutrophil count (ANC)=2.03 to 8.36*10^3/UL
    - Platelet count=140 to 450*10^3/UL
- Have no medical history or evidence of latent tuberculosis infection (LTBI) or active tubercular disease (TB), as evidenced by TB skin test or chest X-ray
- Have an expanded disability status scale (EDSS) from 1.0-5.5, inclusive
- Have no prior exposure to immunosuppressive or cytotoxic agents (with the exception of steroids for MS flare management, or intravenous immunoglobulin-G [IVIG] after allowed wash-out periods
- If female, must:
    - be neither pregnant nor breast-feeding, nor attempting to conceive, and
    - use a highly effective method of contraception throughout the entire duration of the study and for 6 months (6 menstrual cycles) following completion of the last dose of study medication. A highly effective method of contraception is defined as one which result in a low failure rate (that is, less than 1 percent per year) when used consistently and correctly, such as implants, injectables, combined oral contraceptives, some intrauterine devices (IUDs), sexual abstinence or a vasectomized partner. For the purpose of this trial, women of childbearing potential are defined as: All female subjects after puberty unless they are post-menopausal for at least 2 years, or are surgically sterile
- If male, must be willing to use contraception to avoid pregnancies throughout the entire duration of the study and for 90 days following the last dose of study medication
- Be willing and able to comply with study procedures for the duration of the study
- Have not met any of the exclusion criteria outlined below; and
- Have voluntarily provided written informed consent, including, for United states of America (USA), subject authorization under Health Insurance Portability and Accountability Act (HIPAA), prior to any study-related procedure that is not part of normal medical care, and with the understanding that the subject may withdraw consent at any time without prejudice to future medical care
- Other protocol defined inclusion criteria may apply

Exclusion Criteria:

- Has primary progressive multiple sclerosis (PPMS) or SPMS without relapses forms
- Has prior or current malignancy other than medically documented complete excision of basal cell skin cancer no less than 5 years prior to Screening
- Has a history of chronic or clinically significant hematological abnormalities
- Prior use of cladribine, fingolimod, teriflunimide, laquinimod, mitoxantrone, campath-1h, cyclophosphamide, azathioprine, methotrexate, daclizumab, natalizumab, lymphoid irradiation, bone marrow transplantation or myelosuppressive/cytotoxic therapy
- Use of cytokine or anti-cytokine therapy or plasmapheresis within 3 months prior to SD 1
- Treatment with IVIG within 30 days of Screening
- Treatment with oral or parenteral corticosteroids 30 days of Screening
- Treatment with adrenocorticotropic hormone within 28 days prior to SD 1

- Use of any investigational drug (other than Rebif® New Formulation [RNF], Avonex® or Betaferon®) or experimental procedure within 6 months prior to SD 1
- Has inadequate liver function, defined by a total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT) or alkaline phosphatase greater than 2.5 times the upper limit of the normal values
- Suffers from major medical illness such as cardiac, endocrinologic, hepatic, immunologic (other than MS), metabolic, renal, pulmonary, gastrointestinal, dermatologic, or other major disease that would preclude the administration of oral cladribine
- Suffers from major psychiatric illness (including history of, or current, severe depressive disorders and/or suicidal ideation) that in the opinion of the investigator creates undue risk to the subject or could affect compliance with the study protocol
- Has history of active or chronic infectious disease or any disease which compromises immune function (for example, human immunodeficiency virus [HIV]+, human T-lymphotropic virus [HTLV-1], Lyme disease, LTBI or TB)
- Has an allergy or hypersensitivity to gadolinium, to cladribine or any of its excipients, or IFN-beta or any of its excipient(s)
- Has any renal condition that would preclude the administration of gadolinium (for example, acute or chronic severe renal insufficiency [glomerular filtration rate less than 30 milliliter per minute {mL/min} per 1.73 square meter {m^2}])
- Has a positive stool hemoccult test at Screening
- Has a history of seizures not adequately controlled by treatment

Contacts/Locations

Study Officials:

Locations: United States, Massachusetts
US Medical Information
Rockland, Massachusetts, United States, 02370

Italy
Research Site
Milan, Italy

Research Site
Rome, Italy

Research Site
Fidenza, Italy

Research Site
Napoli, Italy

Spain
Research site
Barcelona, Spain

Research Site
Seville, Spain

Research Site

Malaga, Spain

Research Site
Bilbao, Spain

Research Site
Alicante, Spain

Research Site
Madrid, Spain

Research Site
Santiago, Spain

Russian Federation
Research Site
Moscow, Russian Federation

Research Site
St. Petersburg, Russian Federation

Research Site
Arkhangelsk, Russian Federation

Research Site
Kazan, Russian Federation

Research Site
Smolensk, Russian Federation

Research Site
Novosibirsk, Russian Federation

Research Site
Samara, Russian Federation

United States, Florida
Research Site
Tampa, Florida, United States

United States, Texas
Research Site
Round Rock, Texas, United States

United States, California
Research Site

Los Angeles, California, United States

United States, North Carolina
Research Site
Charlote, North Carolina, United States

United States, Pennsylvania
Research Site
Philadelphia, Pennsylvania, United States

United States, Colorado
Research Site
Fort Collins, Colorado, United States

United States, Tennessee
Research Site
Nashville, Tennessee, United States

United States, Texas
Research Site
Houston, Texas, United States

United States, Missouri
Research Site
St Louis, Missouri, United States

United States, North Carolina
Research Site
Winston-Salem, North Carolina, United States

United States, Arizona
Research Site
Scottsdale, Arizona, United States

United States, Vermont
Research Site
Burlington, Vermont, United States

United States, Arizona
Research Site
Phoenix, Arizona, United States

Research Site
Phoenix, Arizona, United States

United States, New Mexico

Research Site
Albuquerque, New Mexico, United States

United States, New Jersey
Research Site
Newark, New Jersey, United States

United States, Massachusetts
Research Site
Boston, Massachusetts, United States

United States, Colorado
Research Site
Boulder, Colorado, United States

United States, Georgia
Research Site
Atlanta, Georgia, United States

United States, Illinois
Research Site
Peoria, Illinois, United States

United States, Pennsylvania
Research Site
Bethlehem, Pennsylvania, United States

United States, Alabama
Research Site
Cullman, Alabama, United States

References

Citations:

Links:

Study Data/Documents:

Participant Flow

Pre-Assignment Details	Initially 42 participants were enrolled and randomized under original protocol but enrollment was terminated because early safety signals related to hematological toxicities. Protocol Amendment 1 and 2 was implemented and 172 participants were enrolled. Results of participants enrolled under Amendment 1 and 2 are reported.

Reporting Groups

	Description
Cladribine 3.5 mg/kg, IFN-beta (DB Period)	Participants received cladribine tablets orally as cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total cladribine dose of 3.5 mg/kg along with IFN-beta therapy (Rebif® new formulation [RNF] 44 microgram [mcg] three times a week, subcutaneously; Avonex® 30 mcg every week, intramuscularly; or Betaseron® 250 mcg every other day, subcutaneously) during the double blind (DB) period of 96 weeks.
Placebo, IFN-beta (DB Period)	Participants received matching placebo tablets orally as cumulative dose of 0.875 mg/kg over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total matching placebo dose of 3.5 mg/kg along with IFN-beta therapy (RNF 44 mcg three times a week, subcutaneously; Avonex® 30 mcg every week, intramuscularly; or Betaseron® 250 mcg every other day, subcutaneously) during the DB period of 96 weeks.
Cladribine 3.5 mg/kg, IFN-beta, Cladribine 3.5 mg/kg (OL Ext)	Participants who received cladribine 3.5 mg/kg initially and completed DB period entered in the open label (OL) extension (Ext.) period. In OL Ext. period, participant who met the eligibility criteria received OL oral cladribine 3.5 mg/kg over maximum of 48 weeks along with IFN-beta therapy (RNF 44 mcg three times a week, subcutaneously; Avonex® 30 mcg every week, intramuscularly; or Betaseron® 250 mcg every other day, subcutaneously) up to 48 weeks.
Placebo, IFN-beta, Cladribine 3.5 mg/kg (OL Ext)	Participants who received placebo initially and completed DB period entered in the OL Ext. period. In OL Ext. period, participant who met the eligibility criteria received OL oral cladribine 3.5 mg/kg over maximum of 48 weeks along with IFN-beta therapy (RNF 44 mcg three times a week, subcutaneously; Avonex® 30 mcg every week, intramuscularly; or Betaseron® 250 mcg every other day, subcutaneously) up to 48 weeks.
Cladribine 3.5 mg/kg, IFN-beta (Safety Follow up)	Participants who received cladribine 3.5 mg/kg initially and completed DB period entered in the OL ext. safety follow up period. In this period, participants who did not meet eligibility criteria received only IFN-beta therapy (RNF 44 mcg three times a week, subcutaneously; Avonex® 30 mcg every week, intramuscularly; or Betaseron® 250 mcg every other day, subcutaneously) up to 48 weeks.
Placebo, IFN-beta (Safety Follow up)	Participants who received placebo initially and completed DB period entered in the OL ext. safety follow up period. In this period, participants who did not meet eligibility criteria received only IFN-beta therapy (RNF 44 mcg three times a week, subcutaneously; Avonex® 30 mcg every week, intramuscularly; or Betaseron® 250 mcg every other day, subcutaneously) up to 48 weeks.

Double Blind Period

	Cladribine 3.5 mg/kg, IFN-beta (DB Period)	Placebo, IFN-beta (DB Period)	Cladribine 3.5 mg/kg, IFN-beta, Cladribine 3.5 mg/kg (OL Ext)	Placebo, IFN-beta, Cladribine 3.5 mg/kg (OL Ext)	Cladribine 3.5 mg/kg, IFN-beta (Safety Follow up)	Placebo, IFN-beta (Safety Follow up)
Started	124	48	0	0	0	0
Completed	111	37	0	0	0	0
Not Completed	13	11	0	0	0	0
Adverse Event	2	0	0	0	0	0
Protocol Violation	1	0	0	0	0	0
Unspecified	10	11	0	0	0	0

Ext. Period (With Cladribine Treatment)

	Cladribine 3.5 mg/kg, IFN-beta (DB Period)	Placebo, IFN-beta (DB Period)	Cladribine 3.5 mg/kg, IFN-beta, Cladribine 3.5 mg/kg (OL Ext)	Placebo, IFN-beta, Cladribine 3.5 mg/kg (OL Ext)	Cladribine 3.5 mg/kg, IFN-beta (Safety Follow up)	Placebo, IFN-beta (Safety Follow up)
Started	0	0	47	28	0	0
Completed	0	0	3	4	0	0
Not Completed	0	0	44	24	0	0
Sponsor's decision to terminate study	0	0	44	24	0	0

Ext. Period (No Cladribine Treatment)

	Cladribine 3.5 mg/kg, IFN-beta (DB Period)	Placebo, IFN-beta (DB Period)	Cladribine 3.5 mg/kg, IFN-beta, Cladribine 3.5 mg/kg (OL Ext)	Placebo, IFN-beta, Cladribine 3.5 mg/kg (OL Ext)	Cladribine 3.5 mg/kg, IFN-beta (Safety Follow up)	Placebo, IFN-beta (Safety Follow up)
Started	0	0	0	0	52	7
Completed	0	0	0	0	1	0
Not Completed	0	0	0	0	51	7

	Cladribine 3.5 mg/kg, IFN-beta (DB Period)	Placebo, IFN-beta (DB Period)	Cladribine 3.5 mg/kg, IFN-beta, Cladribine 3.5 mg/kg (OL Ext)	Placebo, IFN-beta, Cladribine 3.5 mg/kg (OL Ext)	Cladribine 3.5 mg/kg, IFN-beta (Safety Follow up)	Placebo, IFN-beta (Safety Follow up)
Sponsor's decision to terminate study	0	0	0	0	51	7

Baseline Characteristics

Reporting Groups

	Description
Cladribine 3.5 mg/kg, IFN-beta	Participants received cladribine tablets orally as cumulative dose of 0.875 milligram per kilogram (mg/kg) over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total cladribine dose of 3.5 mg/kg along with IFN-beta therapy (Rebif® new formulation [RNF] 44 microgram [mcg] three times a week, subcutaneously; Avonex® 30 mcg every week, intramuscularly; or Betaseron® 250 mcg every other day, subcutaneously) during the double blind (DB) period of 96 weeks. After completing DB period, participants entered in OL extension period. In OL extension period, participant who met eligibility criteria received OL oral cladribine 3.5 mg/kg and participants who did not meet the eligibility criteria received IFN-beta only and were followed for safety only.
Placebo, IFN-beta	Participants received matching placebo tablets orally as cumulative dose of 0.875 mg/kg over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total matching placebo dose of 3.5 mg/kg along with IFN-beta therapy (RNF 44 mcg three times a week, subcutaneously; Avonex® 30 mcg every week, intramuscularly; or Betaseron® 250 mcg every other day, subcutaneously) during the double blind (DB) period of 96 weeks. After completing DB period, participants entered in OL extension period. In OL extension period, participant who met eligibility criteria received OL oral cladribine 3.5 mg/kg and participants participants who did not meet the eligibility criteria received IFN-beta only and were followed for safety only.

Baseline Measures

	Cladribine 3.5 mg/kg, IFN-beta	Placebo, IFN-beta	Total
Number of Participants	124	48	172
Age, Continuous [units: years] Mean (Standard Deviation)	38.5 (10.2)	40.1 (10.3)	38.9 (10.2)
Gender, Male/Female [units: participants]			
Female	84	36	120
Male	40	12	52

	Cladribine 3.5 mg/kg, IFN-beta	Placebo, IFN-beta	Total
Time (years) from first attack to study Day 1 [units: years] Mean (Standard Deviation)	9.98 (7.24)	10.83 (7.98)	10.22 (7.44)
Expanded disability status scale (EDSS) score [1] [units: unit on scale] Mean (Standard Deviation)	2.9 (1.2)	3.0 (1.2)	2.9 (1.2)
Number of Gadolinium-enhanced lesions [units: lesions] Mean (Standard Deviation)	1.1 (4.0)	0.6 (1.2)	0.9 (3.4)
Number of Time constant 1 (T1) hypointense lesions [units: lesions] Mean (Standard Deviation)	9.0 (9.2)	9.3 (9.9)	9.1 (9.3)

[1] 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.

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Number of Participants With Adverse Events (AEs) and Serious Adverse Events (SAEs)
Measure Description	An AE was defined as any untoward medical occurrence in the form of signs, symptoms, abnormal laboratory findings, or diseases that emerges or worsens relative to baseline during a clinical study with an Investigational Medicinal Product (IMP), regardless of causal relationship and even if no IMP has been administered. SAE: Any AE that resulted in death; was life threatening; resulted in persistent/significant disability/incapacity; resulted in/prolonged an existing in-patient hospitalization; was a congenital anomaly/birth defect; or was a medically important condition.
Time Frame	Baseline up to Week 96
Safety Issue?	Yes

Analysis Population Description

Safety population included all randomized participants who received at least one dose of study medication in the DB period and had follow-up safety data.

Reporting Groups

	Description
Cladribine 3.5 mg/kg, IFN-beta (DB Period)	Participants received cladribine tablets orally as cumulative dose of 0.875 mg/kg over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total cladribine dose of 3.5 mg/kg along with IFN-beta therapy (RNF 44 mcg three times a week, subcutaneously; Avonex® 30 mcg every week, intramuscularly; or Betaseron® 250 mcg every other day, subcutaneously) during the DB period of 96 weeks.
Placebo, IFN-beta (DB Period)	Participants received matching placebo tablets orally as cumulative dose of 0.875 mg/kg over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total matching placebo dose of 3.5 mg/kg along with IFN-beta therapy (RNF 44 mcg three times a week, subcutaneously; Avonex® 30 mcg every week, intramuscularly; or Betaseron® 250 mcg every other day, subcutaneously) during the DB period of 96 weeks.

Measured Values

	Cladribine 3.5 mg/kg, IFN-beta (DB Period)	Placebo, IFN-beta (DB Period)
Number of Participants Analyzed	124	48
Number of Participants With Adverse Events (AEs) and Serious Adverse Events (SAEs) [units: Participants]		
AEs	119	36
SAEs	12	5

2. Primary Outcome Measure:

Measure Title	Percentage of Participants With Grade 3 or 4 (Common Terminology Criteria for Adverse Events [CTCAE]) Hematological or Liver Toxicity
Measure Description	Percentage of participants with Grade 3 or 4 CTCAE toxicity on the following hematology and liver function parameters were reported: lymphocytes, cluster of differentiation 4 (CD4) cell, neutrophils, white blood cells, hemoglobin, Alanine transaminase (ALT) and Aspartate transaminase (AST). According to CTCAE: Grade 1=mild, Grade 2=moderate, Grade 3=severe, Grade 4=life threatening or disabling and Grade 5=Death
Time Frame	Baseline up to Week 96
Safety Issue?	Yes

Analysis Population Description

Safety population included all randomized participants who received at least one dose of study medication in the DB period and had follow-up safety data.

Reporting Groups

	Description
Cladribine 3.5 mg/kg, IFN-beta (DB Period)	Participants received cladribine tablets orally as cumulative dose of 0.875 mg/kg over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total cladribine dose of 3.5 mg/kg along with IFN-beta therapy (RNF 44 mcg three times a week, subcutaneously; Avonex® 30 mcg every week, intramuscularly; or Betaseron® 250 mcg every other day, subcutaneously) during the DB period of 96 weeks.
Placebo, IFN-beta (DB Period)	Participants received matching placebo tablets orally as cumulative dose of 0.875 mg/kg over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total matching placebo dose of 3.5 mg/kg along with IFN-beta therapy (RNF 44 mcg three times a week, subcutaneously; Avonex® 30 mcg every week, intramuscularly; or Betaseron® 250 mcg every other day, subcutaneously) during the DB period of 96 weeks.

Measured Values

	Cladribine 3.5 mg/kg, IFN-beta (DB Period)	Placebo, IFN-beta (DB Period)
Number of Participants Analyzed	124	48
Percentage of Participants With Grade 3 or 4 (Common Terminology Criteria for Adverse Events [CTCAE]) Hematological or Liver Toxicity [units: Percentage of participants]		
Grade 3 or 4 Lymphocyte toxicity	63.71	2.08
Grade 3 or 4 Hemoglobin toxicity	2.42	0.00
Grade 3 or 4 White Blood Cell toxicity	10.48	0.00
Grade 3 or 4 Neutrophil toxicity	12.10	2.08
Grade 3 or 4 CD4 toxicity	50.81	2.08
Grade 3 or 4 AST toxicity	0.81	0.00
Grade 3 or 4 ALT toxicity	0.81	2.08

3. Primary Outcome Measure:

Measure Title	Percentage of Participants With Adverse Events in Infections and Infestations System Organ Class (SOC)
Measure Description	Adverse Events were entered in infections and infestations SOC as per medical dictionary for regulatory activities (MedDRA) version 11.0
Time Frame	Baseline up to Week 96
Safety Issue?	Yes

Analysis Population Description

Safety population included all randomized participants who received at least one dose of study medication in the DB period and had follow-up safety data.

Reporting Groups

	Description
Cladribine 3.5 mg/kg, IFN-beta (DB Period)	Participants received cladribine tablets orally as cumulative dose of 0.875 mg/kg over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total cladribine dose of 3.5 mg/kg along with IFN-beta therapy (RNF 44 mcg three times a week, subcutaneously; Avonex® 30 mcg every week, intramuscularly; or Betaseron® 250 mcg every other day, subcutaneously) during the DB period of 96 weeks.
Placebo, IFN-beta (DB Period)	Participants received matching placebo tablets orally as cumulative dose of 0.875 mg/kg over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total matching placebo dose of 3.5 mg/kg along with IFN-beta therapy (RNF 44 mcg three times a week, subcutaneously; Avonex® 30 mcg every week, intramuscularly; or Betaseron® 250 mcg every other day, subcutaneously) during the DB period of 96 weeks.

Measured Values

	Cladribine 3.5 mg/kg, IFN-beta (DB Period)	Placebo, IFN-beta (DB Period)
Number of Participants Analyzed	124	48
Percentage of Participants With Adverse Events in Infections and Infestations System Organ Class (SOC) [units: Percentage of participants]	61.3	54.2

4. Secondary Outcome Measure:

Measure Title	Number of Qualifying Relapses
Measure Description	A qualifying relapse was defined as a 2-grade increase in at least one, or a 1-grade increase in at least two, Kurtzke Functional Systems excluding bowel/bladder or cognition changes, in the absence of fever lasting more than or equal to 24 hours, and preceded by more than or equal to 30 days of clinical stability or improvement.
Time Frame	Baseline up to Week 96
Safety Issue?	No

Analysis Population Description

ITT population included all randomized participants who had received at least one dose of study medication in the DB period.

Reporting Groups

	Description
Cladribine 3.5 mg/kg, IFN-beta (DB Period)	Participants received cladribine tablets orally as cumulative dose of 0.875 mg/kg over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total cladribine dose of 3.5 mg/kg along with IFN-beta therapy (RNF 44 mcg three times a week, subcutaneously; Avonex® 30 mcg every week, intramuscularly; or Betaseron® 250 mcg every other day, subcutaneously) during the DB period of 96 weeks.
Placebo, IFN-beta (DB Period)	Participants received matching placebo tablets orally as cumulative dose of 0.875 mg/kg over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total matching placebo dose of 3.5 mg/kg along with IFN-beta therapy (RNF 44 mcg three times a week, subcutaneously; Avonex® 30 mcg every week, intramuscularly; or Betaseron® 250 mcg every other day, subcutaneously) during the DB period of 96 weeks.

Measured Values

	Cladribine 3.5 mg/kg, IFN-beta (DB Period)	Placebo, IFN-beta (DB Period)
Number of Participants Analyzed	124	48
Number of Qualifying Relapses [units: Relapses] Mean (Standard Deviation)	0.23 (0.53)	0.54 (0.87)

Statistical Analysis 1 for Number of Qualifying Relapses

Statistical Analysis Overview	Comparison Groups	Cladribine 3.5 mg/kg, IFN-beta (DB Period), Placebo, IFN-beta (DB Period)
	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]
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Other [Relative Risk]
	Estimated Value	0.38
	Confidence Interval	(2-Sided) 95% 0.23 to 0.65

	Estimation Comments	[Not specified]

5. Secondary Outcome Measure:

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

Analysis Population Description

ITT population included all randomized participants who had received at least one dose of study medication in the DB period.

Reporting Groups

	Description
Cladribine 3.5 mg/kg, IFN-beta (DB Period)	Participants received cladribine tablets orally as cumulative dose of 0.875 mg/kg over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total cladribine dose of 3.5 mg/kg along with IFN-beta therapy (RNF 44 mcg three times a week, subcutaneously; Avonex® 30 mcg every week, intramuscularly; or Betaseron® 250 mcg every other day, subcutaneously) during the DB period of 96 weeks.
Placebo, IFN-beta (DB Period)	Participants received matching placebo tablets orally as cumulative dose of 0.875 mg/kg over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total matching placebo dose of 3.5 mg/kg along with IFN-beta therapy (RNF 44 mcg three times a week, subcutaneously; Avonex® 30 mcg every week, intramuscularly; or Betaseron® 250 mcg every other day, subcutaneously) during the DB period of 96 weeks.

Measured Values

	Cladribine 3.5 mg/kg, IFN-beta (DB Period)	Placebo, IFN-beta (DB Period)
Number of Participants Analyzed	124	48
Number of Combined Unique Active (CUA) Lesions, Active Time Constant 2 (T2) Lesions, and Time Constant 1 (T1) Gadolinium Enhanced (Gd+) Lesions Per Participant Per Scan [units: Lesions] Mean (Standard Deviation)		
T1 Gd+ lesions	0.06 (0.37)	0.34 (0.87)
CUA lesions	0.55 (1.27)	1.12 (1.94)
T2 lesions	0.53 (1.26)	1.04 (1.81)

6. Secondary Outcome Measure:

Measure Title	Annualized Qualifying Relapse Rate
Measure Description	A qualifying relapse was defined as a 2-grade increase in at least one, or a 1-grade increase in at least two, Kurtzke Functional Systems excluding bowel/bladder or cognition changes, in the absence of fever lasting more than or equal to 24 hours, and preceded by more than or equal to 30 days of clinical stability or improvement. The annualized relapse rate for each treatment group was the mean of the annualized relapse rates for all the participants in the group, calculated as the total number of confirmed relapses divided by the total number of days on study multiplied by 365.25.
Time Frame	Baseline up to Week 96
Safety Issue?	No

Analysis Population Description

ITT population included all randomized participants who had received at least one dose of study medication in the DB period.

Reporting Groups

	Description
Cladribine 3.5 mg/kg, IFN-beta (DB Period)	Participants received cladribine tablets orally as cumulative dose of 0.875 mg/kg over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total cladribine dose of 3.5 mg/kg along with IFN-beta therapy (RNF 44 mcg three times a week, subcutaneously; Avonex® 30 mcg every week, intramuscularly; or Betaseron® 250 mcg every other day, subcutaneously) during the DB period of 96 weeks.
Placebo, IFN-beta (DB Period)	Participants received matching placebo tablets orally as cumulative dose of 0.875 mg/kg over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total matching placebo dose of 3.5 mg/kg along with IFN-beta therapy (RNF 44 mcg three times a week, subcutaneously; Avonex® 30 mcg every week, intramuscularly; or Betaseron® 250 mcg every other day, subcutaneously) during the DB period of 96 weeks.

Measured Values

	Cladribine 3.5 mg/kg, IFN-beta (DB Period)	Placebo, IFN-beta (DB Period)
Number of Participants Analyzed	124	48
Annualized Qualifying Relapse Rate [units: relapses per year] Number (95% Confidence Interval)	0.13 (0.08 to 0.17)	0.32 (0.20 to 0.44)

Reported Adverse Events

Time Frame	Baseline up to 144 weeks (96 weeks [DB period] and 48 weeks [Ext. period])
Additional Description	An adverse event (AE) was defined as any untoward medical occurrence in the form of signs, symptoms, abnormal laboratory findings, or diseases that emerges or worsens relative to baseline during a clinical study with an Investigational Medicinal Product (IMP), regardless of causal relationship and even if no IMP has been administered.

Reporting Groups

	Description
Cladribine 3.5 mg/kg, IFN-beta (DB Period)	Participants received cladribine tablets orally as cumulative dose of 0.875 mg/kg over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total cladribine dose of 3.5 mg/kg along with IFN-beta therapy (RNF 44 mcg three times a week, subcutaneously; Avonex® 30 mcg every week, intramuscularly; or Betaseron® 250 mcg every other day, subcutaneously) during the DB period of 96 weeks.
Placebo, IFN-beta (DB Period)	Participants received matching placebo tablets orally as cumulative dose of 0.875 mg/kg over a course of 4-5 consecutive days at Week 1, 5, 48, and 52 resulting in total matching placebo dose of 3.5 mg/kg along with IFN-beta therapy (RNF 44 mcg three times a week, subcutaneously; Avonex® 30 mcg every week, intramuscularly; or Betaseron® 250 mcg every other day, subcutaneously) during the DB period of 96 weeks.
Cladribine 3.5 mg/kg, IFN-beta, Cladribine 3.5 mg/kg (OL Ext)	Participants who received cladribine 3.5 mg/kg initially and completed DB period entered in the open label (OL) extension (Ext.) period. In OL Ext. period, participant who met the eligibility criteria received OL oral cladribine 3.5 mg/kg over maximum of 48 weeks along with IFN-beta therapy (RNF 44 mcg three times a week, subcutaneously; Avonex® 30 mcg every week, intramuscularly; or Betaseron® 250 mcg every other day, subcutaneously) up to 48 weeks.
Placebo, IFN-beta, Cladribine 3.5 mg/kg (OL Ext)	Participants who received placebo initially and completed DB period entered in the OL Ext. period. In OL Ext. period, participant who met the eligibility criteria received OL oral cladribine 3.5 mg/kg over maximum of 48 weeks along with IFN-beta therapy (RNF 44 mcg three times a week, subcutaneously; Avonex® 30 mcg every week, intramuscularly; or Betaseron® 250 mcg every other day, subcutaneously) up to 48 weeks.
Cladribine 3.5 mg/kg, IFN-beta (Safety Follow up)	Participants who received cladribine 3.5 mg/kg initially and completed DB period entered in the OL ext. safety follow up period. In this period, participants who did not meet eligibility criteria received only IFN-beta therapy (RNF 44 mcg three times a week, subcutaneously; Avonex® 30 mcg every week, intramuscularly; or Betaseron® 250 mcg every other day, subcutaneously) up to 48 weeks.
Placebo, IFN-beta (Safety Follow up)	Participants who received placebo initially and completed DB period entered in the OL ext. safety follow up period. In this period, participants who did not meet eligibility criteria received only IFN-beta therapy (RNF 44 mcg three times a week, subcutaneously; Avonex® 30 mcg every week, intramuscularly; or Betaseron® 250 mcg every other day, subcutaneously) up to 48 weeks.

Serious Adverse Events

	Cladribine 3.5 mg/kg, IFN-beta (DB Period)	Placebo, IFN-beta (DB Period)	Cladribine 3.5 mg/kg, IFN-beta, Cladribine 3.5 mg/kg (OL Ext)	Placebo, IFN-beta, Cladribine 3.5 mg/ kg (OL Ext)	Cladribine 3.5 mg/kg, IFN-beta (Safety Follow up)	Placebo, IFN-beta (Safety Follow up)
	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)
Total	12/124 (9.68%)	5/48 (10.42%)	0/47 (0%)	1/28 (3.57%)	1/52 (1.92%)	0/7 (0%)
Gastrointestinal disorders						
Anal fissure [A] *	1/124 (0.81%)	0/48 (0%)	0/47 (0%)	0/28 (0%)	0/52 (0%)	0/7 (0%)
Pancreatitis acute [A] *	1/124 (0.81%)	0/48 (0%)	0/47 (0%)	0/28 (0%)	1/52 (1.92%)	0/7 (0%)
General disorders						
Non-cardiac chest pain [A] *	0/124 (0%)	1/48 (2.08%)	0/47 (0%)	0/28 (0%)	0/52 (0%)	0/7 (0%)
Hepatobiliary disorders						
Cholecystitis [A] *	2/124 (1.61%)	0/48 (0%)	0/47 (0%)	0/28 (0%)	0/52 (0%)	0/7 (0%)
Hepatic cyst [A] *	0/124 (0%)	1/48 (2.08%)	0/47 (0%)	0/28 (0%)	0/52 (0%)	0/7 (0%)
Infections and infestations						
Genital herpes [A] *	1/124 (0.81%)	0/48 (0%)	0/47 (0%)	0/28 (0%)	0/52 (0%)	0/7 (0%)
Human ehrlichiosis [A] *	1/124 (0.81%)	0/48 (0%)	0/47 (0%)	0/28 (0%)	0/52 (0%)	0/7 (0%)
Pyelonephritis acute [A] *	1/124 (0.81%)	0/48 (0%)	0/47 (0%)	0/28 (0%)	0/52 (0%)	0/7 (0%)
Urinary tract infection [A] *	1/124 (0.81%)	0/48 (0%)	0/47 (0%)	0/28 (0%)	0/52 (0%)	0/7 (0%)
Injury, poisoning and procedural complications						
Traumatic haematoma [A] *	0/124 (0%)	0/48 (0%)	0/47 (0%)	1/28 (3.57%)	0/52 (0%)	0/7 (0%)
Ulna fracture [A] *	0/124 (0%)	0/48 (0%)	0/47 (0%)	1/28 (3.57%)	0/52 (0%)	0/7 (0%)
Musculoskeletal and connective tissue disorders						
Arthralgia [A] *	0/124 (0%)	0/48 (0%)	0/47 (0%)	1/28 (3.57%)	0/52 (0%)	0/7 (0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						

	Cladribine 3.5 mg/kg, IFN-beta (DB Period)	Placebo, IFN-beta (DB Period)	Cladribine 3.5 mg/kg, IFN-beta, Cladribine 3.5 mg/kg (OL Ext)	Placebo, IFN-beta, Cladribine 3.5 mg/ kg (OL Ext)	Cladribine 3.5 mg/kg, IFN-beta (Safety Follow up)	Placebo, IFN-beta (Safety Follow up)
	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)
Benign breast neoplasm [A] *	1/124 (0.81%)	0/48 (0%)	0/47 (0%)	0/28 (0%)	0/52 (0%)	0/7 (0%)
Lipoma [A] *	1/124 (0.81%)	0/48 (0%)	0/47 (0%)	0/28 (0%)	0/52 (0%)	0/7 (0%)
Melanocytic naevus [A] *	1/124 (0.81%)	0/48 (0%)	0/47 (0%)	0/28 (0%)	0/52 (0%)	0/7 (0%)
Seborrhoeic keratosis [A] *	1/124 (0.81%)	0/48 (0%)	0/47 (0%)	0/28 (0%)	0/52 (0%)	0/7 (0%)
Skin papilloma [A] *	1/124 (0.81%)	0/48 (0%)	0/47 (0%)	0/28 (0%)	0/52 (0%)	0/7 (0%)
Nervous system disorders						
Grand mal convulsion [A] *	1/124 (0.81%)	0/48 (0%)	0/47 (0%)	0/28 (0%)	0/52 (0%)	0/7 (0%)
Status epilepticus [A] *	1/124 (0.81%)	0/48 (0%)	0/47 (0%)	0/28 (0%)	0/52 (0%)	0/7 (0%)
Pregnancy, puerperium and perinatal conditions						
Abortion spontaneous [A] *	0/124 (0%)	1/48 (2.08%)	0/47 (0%)	0/28 (0%)	0/52 (0%)	0/7 (0%)
Renal and urinary disorders						
Atonic urinary bladder [A] *	1/124 (0.81%)	0/48 (0%)	0/47 (0%)	0/28 (0%)	0/52 (0%)	0/7 (0%)
Hydronephrosis [A] *	1/124 (0.81%)	0/48 (0%)	0/47 (0%)	0/28 (0%)	0/52 (0%)	0/7 (0%)
Nephrolithiasis [A] *	1/124 (0.81%)	0/48 (0%)	0/47 (0%)	0/28 (0%)	0/52 (0%)	0/7 (0%)
Reproductive system and breast disorders						
Menometrorrhagia [A] *	1/124 (0.81%)	0/48 (0%)	0/47 (0%)	0/28 (0%)	0/52 (0%)	0/7 (0%)
Skin and subcutaneous tissue disorders						
Skin lesion [A] *	0/124 (0%)	1/48 (2.08%)	0/47 (0%)	0/28 (0%)	0/52 (0%)	0/7 (0%)
Surgical and medical procedures						
Abortion induced [A] *	0/124 (0%)	1/48 (2.08%)	0/47 (0%)	0/28 (0%)	0/52 (0%)	0/7 (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 3.5 mg/kg, IFN-beta (DB Period)	Placebo, IFN-beta (DB Period)	Cladribine 3.5 mg/kg, IFN-beta, Cladribine 3.5 mg/kg (OL Ext)	Placebo, IFN-beta, Cladribine 3.5 mg/ kg (OL Ext)	Cladribine 3.5 mg/kg, IFN-beta (Safety Follow up)	Placebo, IFN-beta (Safety Follow up)
	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)
Total	111/124 (89.52%)	33/48 (68.75%)	24/47 (51.06%)	12/28 (42.86%)	0/52 (0%)	0/7 (0%)
Blood and lymphatic system disorders						
Leukopenia [A] *	14/124 (11.29%)	0/48 (0%)	0/47 (0%)	0/28 (0%)	0/52 (0%)	0/7 (0%)
Lymphopenia [A] *	50/124 (40.32%)	0/48 (0%)	11/47 (23.4%)	2/28 (7.14%)	0/52 (0%)	0/7 (0%)
Neutropenia [A] *	13/124 (10.48%)	3/48 (6.25%)	3/47 (6.38%)	3/28 (10.71%)	0/52 (0%)	0/7 (0%)
Gastrointestinal disorders						
Diarrhoea [A] *	9/124 (7.26%)	1/48 (2.08%)	0/47 (0%)	0/28 (0%)	0/52 (0%)	0/7 (0%)
Dyspepsia [A] *	2/124 (1.61%)	3/48 (6.25%)	0/47 (0%)	0/28 (0%)	0/52 (0%)	0/7 (0%)
Nausea [A] *	18/124 (14.52%)	6/48 (12.5%)	0/47 (0%)	0/28 (0%)	0/52 (0%)	0/7 (0%)
Vomiting [A] *	4/124 (3.23%)	3/48 (6.25%)	0/47 (0%)	0/28 (0%)	0/52 (0%)	0/7 (0%)
General disorders						
Fatigue [A] *	7/124 (5.65%)	3/48 (6.25%)	0/47 (0%)	0/28 (0%)	0/52 (0%)	0/7 (0%)
Influenza like illness [A] *	13/124 (10.48%)	4/48 (8.33%)	0/47 (0%)	0/28 (0%)	0/52 (0%)	0/7 (0%)
Pain [A] *	2/124 (1.61%)	4/48 (8.33%)	0/47 (0%)	0/28 (0%)	0/52 (0%)	0/7 (0%)
Pyrexia [A] *	13/124 (10.48%)	4/48 (8.33%)	0/47 (0%)	0/28 (0%)	0/52 (0%)	0/7 (0%)

	Cladribine 3.5 mg/kg, IFN-beta (DB Period)	Placebo, IFN-beta (DB Period)	Cladribine 3.5 mg/kg, IFN-beta, Cladribine 3.5 mg/kg (OL Ext)	Placebo, IFN-beta, Cladribine 3.5 mg/ kg (OL Ext)	Cladribine 3.5 mg/kg, IFN-beta (Safety Follow up)	Placebo, IFN-beta (Safety Follow up)
	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)
Infections and infestations						
Bronchitis [A] *	7/124 (5.65%)	2/48 (4.17%)	0/47 (0%)	0/28 (0%)	0/52 (0%)	0/7 (0%)
Herpes zoster [A] *	7/124 (5.65%)	0/48 (0%)	0/47 (0%)	0/28 (0%)	0/52 (0%)	0/7 (0%)
Influenza [A] *	7/124 (5.65%)	4/48 (8.33%)	0/47 (0%)	0/28 (0%)	0/52 (0%)	0/7 (0%)
Nasopharyngitis [A] *	28/124 (22.58%)	8/48 (16.67%)	3/47 (6.38%)	0/28 (0%)	0/52 (0%)	0/7 (0%)
Sinusitis [A] *	15/124 (12.1%)	6/48 (12.5%)	0/47 (0%)	0/28 (0%)	0/52 (0%)	0/7 (0%)
Upper respiratory tract infection [A] *	14/124 (11.29%)	8/48 (16.67%)	3/47 (6.38%)	1/28 (3.57%)	0/52 (0%)	0/7 (0%)
Urinary tract infection [A] *	14/124 (11.29%)	5/48 (10.42%)	1/47 (2.13%)	4/28 (14.29%)	0/52 (0%)	0/7 (0%)
Injury, poisoning and procedural complications						
Fall [A] *	0/124 (0%)	0/48 (0%)	1/47 (2.13%)	2/28 (7.14%)	0/52 (0%)	0/7 (0%)
Investigations						
Alanine aminotransferase increased [A] *	2/124 (1.61%)	3/48 (6.25%)	0/47 (0%)	0/28 (0%)	0/52 (0%)	0/7 (0%)
Lymphocyte count decreased [A] *	13/124 (10.48%)	0/48 (0%)	4/47 (8.51%)	1/28 (3.57%)	0/52 (0%)	0/7 (0%)
Musculoskeletal and connective tissue disorders						
Arthralgia [A] *	8/124 (6.45%)	2/48 (4.17%)	0/47 (0%)	0/28 (0%)	0/52 (0%)	0/7 (0%)
Back pain [A] *	10/124 (8.06%)	4/48 (8.33%)	0/47 (0%)	0/28 (0%)	0/52 (0%)	0/7 (0%)
Pain in extremity [A] *	12/124 (9.68%)	0/48 (0%)	0/47 (0%)	0/28 (0%)	0/52 (0%)	0/7 (0%)
Nervous system disorders						

	Cladribine 3.5 mg/kg, IFN-beta (DB Period)	Placebo, IFN-beta (DB Period)	Cladribine 3.5 mg/kg, IFN-beta, Cladribine 3.5 mg/kg (OL Ext)	Placebo, IFN-beta, Cladribine 3.5 mg/ kg (OL Ext)	Cladribine 3.5 mg/kg, IFN-beta (Safety Follow up)	Placebo, IFN-beta (Safety Follow up)
	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)
Dizziness [A] *	6/124 (4.84%)	3/48 (6.25%)	0/47 (0%)	0/28 (0%)	0/52 (0%)	0/7 (0%)
Headache [A] *	31/124 (25%)	10/48 (20.83%)	6/47 (12.77%)	1/28 (3.57%)	0/52 (0%)	0/7 (0%)
Pregnancy, puerperium and perinatal conditions						
Pregnancy [A] *	1/124 (0.81%)	3/48 (6.25%)	0/47 (0%)	0/28 (0%)	0/52 (0%)	0/7 (0%)
Psychiatric disorders						
Depression [A] *	7/124 (5.65%)	2/48 (4.17%)	0/47 (0%)	0/28 (0%)	0/52 (0%)	0/7 (0%)
Insomnia [A] *	5/124 (4.03%)	3/48 (6.25%)	0/47 (0%)	0/28 (0%)	0/52 (0%)	0/7 (0%)
Respiratory, thoracic and mediastinal disorders						
Cough [A] *	8/124 (6.45%)	4/48 (8.33%)	0/47 (0%)	0/28 (0%)	0/52 (0%)	0/7 (0%)
Pharyngolaryngeal pain [A] *	7/124 (5.65%)	3/48 (6.25%)	0/47 (0%)	0/28 (0%)	0/52 (0%)	0/7 (0%)
Sinus congestion [A] *	1/124 (0.81%)	3/48 (6.25%)	0/47 (0%)	0/28 (0%)	0/52 (0%)	0/7 (0%)
Skin and subcutaneous tissue disorders						
Rash [A] *	6/124 (4.84%)	3/48 (6.25%)	0/47 (0%)	0/28 (0%)	0/52 (0%)	0/7 (0%)

* Indicates events were collected by non-systematic methods.

A Term from vocabulary, MedDRA (11.0)

Limitations and Caveats

The 96-week DB treatment period of study was completed as planned, and safety and exploratory efficacy results are presented here. The duration of OL Ext. period was reduced for some participants, following termination of the development program.

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