ClinicalTrials.gov Protocol and Results Registration System (PRS) Receipt
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Comparison of Alemtuzumab and Rebif® Efficacy in Multiple Sclerosis, Study One (CARE-MS I)

This study has been completed.

Sponsor:	Genzyme, a Sanofi Company
Collaborators:	Bayer
Information provided by (Responsible Party):	Sanofi (Genzyme, a Sanofi Company)
ClinicalTrials.gov Identifier:	NCT00530348

Purpose

The purpose of this study was to establish the efficacy and safety of alemtuzumab (Lemtrada™) as a treatment for relapsing-remitting multiple sclerosis (MS), in comparison with subcutaneous (SC) interferon beta-1a (Rebif®). The study had enrolled participants who had not previously received MS disease-modifying therapies. Participants had monthly laboratory tests and comprehensive testing every 3 months.

Condition	Intervention	Phase
Multiple Sclerosis, Relapsing-Remitting	Biological/Vaccine: Alemtuzumab Biological/Vaccine: Interferon beta-1a	Phase 3

Study Type: Interventional
Study Design: Treatment, Parallel Assignment, Single Blind (Outcomes Assessor), Randomized, Safety/Efficacy Study
Official Title: A Phase 3 Randomized, Rater-Blinded Study Comparing Two Annual Cycles of Intravenous Alemtuzumab to Three-Times Weekly Subcutaneous Interferon Beta-1a (Rebif®) in Treatment-Naïve Patients With Relapsing-Remitting Multiple Sclerosis

Further study details as provided by Sanofi (Genzyme, a Sanofi Company):

Primary Outcome Measure:

- Percentage of Participants With Sustained Accumulation of Disability (SAD) [Time Frame: Up to 2 years] [Designated as safety issue: No]

EDSS is an ordinal scale in half-point increments that quantifies disability in participants with MS. It assesses 7 functional systems (visual, brainstem, pyramidal, cerebellar, sensory, bowel/bladder and cerebral) as well as ambulation. EDSS total score: 0 (normal neurological examination) to 10 (death due to MS). As measured by EDSS score, SAD was defined as increase of at least 1.5 points for participants with Baseline score of 0 and increase of at least 1.0 point for participants with a Baseline score of 1.0 or more; and the increase persisted for at least next 2 scheduled assessments, that is, 6 consecutive months. Onset date of SAD was date of first EDSS assessment that began 6 month consecutive period of SAD. Participants who did not reach SAD endpoint were censored at their last visit. Percentage of participants with SAD, estimated by Kaplan-Meier (KM) method, was reported.

- Annualized Relapse Rate [Time Frame: Up to 2 years] [Designated as safety issue: No]
  Relapse was defined as new neurological symptoms or worsening of previous neurological symptoms with an objective change on neurological examination, attributable to multiple sclerosis that lasted for at least 48 hours, that were present at normal body temperature, and that were preceded by at least 30 days of clinical stability. Annualized relapse rate was estimated through negative binomial regression with robust variance estimation and covariate adjustment for geographic region using observed number of relapses as dependent variable, the log total amount of follow-up from date of first study treatment for each participant as an offset variable, and treatment group and geographic region as model covariates.

Secondary Outcome Measures:

- Percentage of Participants Who Were Relapse Free at Year 2 [Time Frame: Year 2] [Designated as safety issue: No]
  Participants were considered relapse free at Year 2 if they did not experience a relapse from the date of first study treatment to study completion at 24 months. Percentage of participants who were relapse free at Year 2, estimated using the KM method, was reported.
- Change From Baseline in Expanded Disability Status Scale (EDSS) Score at Year 2 [Time Frame: Baseline, Year 2] [Designated as safety issue: No]
  EDSS is an ordinal scale in half-point increments that quantifies disability in participants with MS. It assesses the 7 functional systems (visual, brainstem, pyramidal, cerebellar, sensory, bowel/bladder and cerebral) as well as ambulation. EDSS total score ranges from 0 (normal neurological examination) to 10 (death due to MS). Change was calculated by subtracting Baseline value from value at Year 2.
- Change From Baseline in Multiple Sclerosis Functional Composite (MSFC) Score at Year 2 [Time Frame: Baseline, Year 2] [Designated as safety issue: No]
  MSFC is a multidimensional measure consisting of quantitative tests of ambulation (Timed 25-Foot Walk), manual dexterity (9-Hole Peg Test; 9HPT), and cognitive function (Paced Auditory Serial Addition Test; PASAT). The MSFC score was calculated as the mean of the Z-scores of the 3 components. A Z-score was calculated by subtracting the mean of the reference population from the test result, then dividing by the standard deviation of the reference population. Higher Z-scores reflected better neurological function and a positive change from Baseline indicates improvement. An increase in score indicated an improvement (Z-score range: -3 to +3). Acquisition of disability was measured by change from Baseline in MSFC score at Year 2.
- Percent Change From Baseline in Magnetic Resonance Imaging Time Constant 2 (MRI-T2) Hyperintense Lesion Volume at Year 2 [Time Frame: Baseline, Year 2] [Designated as safety issue: No]
  Percent change in MS lesion volume as measured by MRI-T2 scan was calculated from MRI-T2-weighted scans as the following: (lesion volume at 2 years - lesion volume at Baseline)*100/ (lesion volume at Baseline).

Enrollment: 581
Study Start Date: August 2007
Primary Completion Date: April 2011
Study Completion Date: April 2011

Arms	Assigned Interventions
Experimental: Alemtuzumab	Biological/Vaccine: Alemtuzumab Alemtuzumab 12 milligram (mg) per day intravenous (IV) infusion on 5 consecutive days at Month 0,

Arms	Assigned Interventions
	followed by alemtuzumab 12 mg per day IV infusion on 3 consecutive days at Month 12. Other Names: Lemtrada
Active Comparator: Interferon Beta-1a	Biological/Vaccine: Interferon beta-1a Interferon beta-1a 44 microgram (mcg) subcutaneously 3-times weekly for 24 months. Dose adjustment was done as per Investigator's discretion. Other Names: Rebif®

Detailed Description:

Every participant had received active treatment; there was no placebo. Participants who qualified were randomly assigned to treatment with either alemtuzumab or SC interferon beta-1a at a 2:1 ratio (that is, 2 given alemtuzumab for every 1 given interferon beta-1a). Alemtuzumab was administered in two annual courses, once at the beginning of the study and again 1 year later. Interferon beta-1a was self-injected 3 times per week for 2 years. All participants were required to return to their study site every 3 months for neurologic assessment. In addition, safety-related laboratory tests were performed at least monthly. Participation in this study ended 2 years after the start of treatment for each participant. Additionally, participants who received alemtuzumab might be followed in CAMMS03409 (NCT00930553) an extension study for safety and efficacy assessments. Participants who received interferon beta-1a and completed 2 years on study might be eligible to receive alemtuzumab on the extension study.

Eligibility

Ages Eligible for Study: 18 Years to 50 Years
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:

- Given written/signed informed consent
- Age 18 to 50 years old (inclusive) as of the date the informed consent form (ICF) was signed
- Diagnosis of MS per updated McDonald criteria, and cranial magnetic resonance imaging (MRI) scan demonstrating white matter lesions attributable to MS within 5 years of screening
- Onset of MS symptoms (as determined by a neurologist, either at screening or retrospectively) within 5 years of the date the ICF was signed
- Expanded Disability Status Scale (EDSS) score 0.0 to 3.0 (inclusive) at screening
- Greater than or equal to (>=) 2 MS attacks (first episode or relapse) occurring in the 24 months prior to the date the ICF was signed, with >=1 attack in the 12 months prior to the date the ICF was signed, with objective neurological signs confirmed by a physician, nurse practitioner, or other Genzyme-approved health-care provider and the objective signs could be identified retrospectively

Exclusion Criteria:

- Received prior therapy for MS other than corticosteroids, for example, alemtuzumab, interferons, intravenous immunoglobulin, glatiramer acetate, natalizumab, and mitoxantrone
- Exposure to azathioprine, cladribine, cyclophosphamide, cyclosporine A, methotrexate, or any other immunosuppressive agent other than systemic corticosteroid treatment
- Any progressive form of MS
- History of malignancy (except basal skin cell carcinoma)
- CD4 + , CD8 + count, B cell, or absolute neutrophil count less than (<) lower limit of normal (LLN) at screening
- Known bleeding disorder (for example, dysfibrinogenemia, factor IX deficiency, hemophilia, Von Willebrand's disease, disseminated intravascular coagulation, fibrinogen deficiency, or clotting factor deficiency)
- Significant autoimmune disease including but not limited to immune cytopenias, rheumatoid arthritis, systemic lupus erythematosus, other connective tissue disorders, vasculitis, inflammatory bowel disease, severe psoriasis
- Presence of anti-thyroid stimulating hormone (TSH) receptor (TSHR) antibodies (that is, above the LLN)
- Active infection or at high risk for infection

Contacts and Locations

Locations

United States, Alabama
North Central Neurology Associates, P.C.
Cullman, Alabama, United States
United States, Arizona
Barrow Neurological Institute, St. Joseph's Hospital & Medical Center
Phoenix, Arizona, United States
Mayo Clinic Arizona
Scottsdale, Arizona, United States
Northwest NeuroSpecialists, PLLC
Tucson, Arizona, United States
United States, Colorado
Advanced Neurosciences Research
Fort Collins, Colorado, United States
United States, Florida
Neurological Associates
Pompano Beach, Florida, United States
Axiom Clinical Research of Florida
Tampa, Florida, United States
United States, Idaho
Idaho Falls Multiple Sclerosis Center, PLLC
Idaho Falls, Idaho, United States
United States, Illinois
Consultants in Neurology, Ltd.
Northbrook, Illinois, United States
United States, Indiana
Fort Wayne Neurological Center
Fort Wayne, Indiana, United States

United States, Kansas
University of Kansas Medical Center
Kansas City, Kansas, United States
MidAmerican Neuroscience Institute
Lenexa, Kansas, United States
United States, Kentucky
Associates in Neurology, PSC
Lexington, Kentucky, United States
University of Louisville Research Foundation
Louisville, Kentucky, United States
United States, Louisiana
Louisiana State University Health Sciences Center
Shreveport, Louisiana, United States
United States, Massachusetts
UMass Memorial Medical Center
Worcester, Massachusetts, United States
United States, Michigan
University of Michigan Health System
Ann Arbor, Michigan, United States
Wayne State University
Detroit, Michigan, United States
United States, Nevada
University of Nevada School of Medicine
Las Vegas, Nevada, United States
United States, New Hampshire
Dartmouth-Hitchcock Medical Center
Lebanon, New Hampshire, United States
United States, New Mexico
University of New Mexico, Health Sciences Center, MS Specialty Clinic
Albuquerque, New Mexico, United States
United States, New York
Empire Neurology
Latham, New York, United States
Comprehensive Multiple Sclerosis Care Center at South Shore Neurologic Associates, P.C.
Patchogue, New York, United States
University of Rochester Medical Center
Rochester, New York, United States
United States, North Carolina
Carolinas Medical Center (CMC), Neurosciences & Spine Institute (NSSI)
Charlotte, North Carolina, United States
United States, Ohio
The Ohio State University Medical Center, Multiple Sclerosis Center
Columbus, Ohio, United States
Oak Clinic for Multiple Sclerosis
Uniontown, Ohio, United States

United States, Oklahoma
MS Center of Oklahoma
Oklahoma City, Oklahoma, United States
United States, Pennsylvania
Lehigh Valley Hospital Neurosciences and Pain Research
Allentown, Pennsylvania, United States
United States, Tennessee
Advanced Neurosciences Institute
Franklin, Tennessee, United States
Biomedical Research Alliance of NY, LLC
Franklin, Tennessee, United States
Hope Neurology PC
Knoxville, Tennessee, United States
United States, Texas
Baylor College of Medicine, Maxine Mesinger MS Clinic
Houston, Texas, United States
Central Texas Neurology
Round Rock, Texas, United States
Integra Clinical Research
San Antonio, Texas, United States
Neurology Center of San Antonio
San Antonio, Texas, United States
Argentina
DIABAID
Buenos Aires, Argentina
Australia
Concord Repatriation General Hospital
Concord, Australia
Westmead Hospital
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Australia, Queensland
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Australia, South Australia
The Queen Elizabeth Hospital
Woodville South, South Australia, Australia
Australia, Tasmania
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Austin Health

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Hospital Sao Lucas PUC-RS
Porto Alegre, RS, Brazil
Hospital de Clínicas USP
Sao Paulo, SP, Brazil
Canada, Alberta
University of Calgary and Foothills Medical Cenre
Calgary, Alberta, Canada
Canada, British Columbia
UBC Hospital
Vancouver, British Columbia, Canada
Canada, Ontario
The Ottawa Hospital, General Campus
Ottawa, Ontario, Canada
Canada, Quebec
Clinique Nuero-outaouais
Gatineau, Quebec, Canada
Clinique Neuro rive-sud, Recherche Sepmus, Inc.
Greenfield park, Quebec, Canada
Croatia
Clinical Hospital Centre Rijeka
Rijeka, Croatia
General Hospital Varazdin
Varazdin, Croatia
General Hospital "Sveti Duh"
Zagreb, Croatia
Clinical Hospital Centre "Sestre Milosrdnice"
Zagreb, Croatia
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France
Hopital Purpan
Toulouse, France
Germany
Judisches Krankenhaus Berlin

Berlin, Germany
Universitätsklinik Carl Gustav Carus Dresden
Dresden, Germany
Klinikum der Goethe Universität Frankfurt
Frankfurt, Germany
Medizinische Hochschule Hannover
Hannover, Germany
Oberhavelkliniken Hennigsdorf
Hennigsdorf, Germany
Asklepios Klinikum Brandenburg
Teupitz, Germany
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Mexico City, Mexico
Hospital Medica Sur CIF-BIOTEC
Mexico City, Mexico
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Lodz, Poland
Independent Public Teaching Hospital No. 4 in Lublin
Lublin, Poland
Heliodor Swiecicki Teaching Hospital of the Poznan University of Medical Sciences
Poznan, Poland
Russian Federation
Research Medical Complex "Your Health" Ltd
Kazan, Russian Federation
Moscow State Medical Institution City Clinical Hospital #11
Moscow, Russian Federation
Moscow City Hospital #11
Moscow, Russian Federation
Scientific Neurology Center RAMS
Moscow, Russian Federation
Municipal City Hospital #33
Nizhniy Novgorod, Russian Federation
Federal State Institution Siberian Rettitorial Medical Center under Federal Medical-Biological Agency of Russia
Novosibirsk, Russian Federation
City Clinical Hospital #2
Pyatigorsk, Russian Federation
Samara Regional Clinical Hospital n.a. Kalinin
Samara, Russian Federation
Nikolaevskaya Hospital
St. Petersburg, Russian Federation
St. Petersburg Pavlov State Medical University

St. Petersburg, Russian Federation
Institute of Human Brain RAS
St. Petersburg, Russian Federation
State Medical Institution: Republican Clinical Hospital n.a. G.G. Kuvatov
Ufa, Russian Federation
Serbia
Clinical Centre Serbia, Institute for Neurology
Belgrade, Serbia
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Kyiv, Ukraine
Danylo Halytsky Lviv National Medical University
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United Kingdom
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Sheffield, United Kingdom
Department Of Neurosciences, Addenbrookes Hospital
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Centre for Neuroscience & Trauma, Blizard Institute of Cell and Molecular Science, Barts and The London School of Medicine and Dentistry
London, England, United Kingdom
University Hospital of Wales
Cardiff, Wales, United Kingdom

Investigators

Study Director:	Medical Monitor	Genzyme Corporation

More Information

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003718/WC500150521.pdf
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003718/WC5...

Publications:

Cohen JA, Coles AJ, Arnold DL, Confavreux C, Fox EJ, Hartung HP, Havrdova E, Selmaj KW, Weiner HL, Fisher E, Brinar VV, Giovannoni G, Stojanovic M, Ertik BI, Lake SL, Margolin DH, Panzara MA, Compston DA; CARE-MS I investigators. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. Lancet. 2012 Nov 24;380(9856):1819-28. doi: 10.1016/S0140-6736(12)61769-3. Epub 2012 Nov 1.

Responsible Party:	Genzyme, a Sanofi Company
Study ID Numbers:	CAMMS323 ISRCTN21534255 [Registry ID: ISRCTN] ACTRN12608000435381 [Registry ID: ANZCTR] CARE-MS I [NMSS] 2007-001161-14 [EudraCT Number]
Health Authority:	United States: Food and Drug Administration Brazil: National Health Surveillance Agency Argentina: Administracion Nacional de Medicamentos, Alimentos y Tecnologia Medica Australia: Department of Health and Ageing Therapeutic Goods Administration Canada: Health Canada Croatia: Agency for Medicinal Product and Medical Devices Czech Republic: State Institute for Drug Control France: Afssaps - Agence française de sécurité sanitaire des produits de santé (Saint-Denis) Germany: Paul-Ehrlich-Institut Mexico: Federal Commission for Protection Against Health Risks Poland: Office for Registration of Medicinal Products, Medical Devices and Biocidal Products Russia: Ministry of Health of the Russian Federation Serbia and Montenegro: Agency for Drugs and Medicinal Devices Sweden: Medical Products Agency Ukraine: State Pharmacological Center - Ministry of Health United Kingdom: Medicines and Healthcare Products Regulatory Agency

Participant Flow

Recruitment Details	Participants were screened at 101 investigational sites in Argentina, Australia, Brazil, Canada, Croatia, the Czech Republic, France, Germany, Mexico, Poland, Russia, Serbia, Sweden, Ukraine, the United Kingdom (UK), and the United States (US) between August 28, 2007 and April 27, 2011.

Reporting Groups

	Description
Interferon Beta-1a	Interferon beta-1a (Rebif®) 44 microgram (mcg) subcutaneously 3-times weekly for 24 months. Dose adjustment was done as per Investigator's discretion.
Alemtuzumab	Alemtuzumab (Lemtrada™) 12 milligram (mg) per day intravenous (IV) infusion on 5 consecutive days at Month 0, followed by alemtuzumab 12 mg per day IV infusion on 3 consecutive days at Month 12.

Overall Study

	Interferon Beta-1a	Alemtuzumab
Started	195 [1]	386 [1]
Treated	187 [2]	376 [2]
Completed	173	367
Not Completed	22	19
Adverse Event	5	1
Death	0	1
Lack of Efficacy	2	0
Lost to Follow-up	0	2
Physician Decision	1	2
Pregnancy	1	0
Withdrawal by Subject	12	12
Randomised in error	1	0
Noncompliance with inclusion criterion 3	0	1

[1] Randomized.
[2] All randomized participants who received at least 1 dose of study drug.

Baseline Characteristics

Analysis Population Description

Full analysis set (FAS) population included all randomized participants who received at least 1 dose of study drug.

Reporting Groups

	Description
Interferon Beta-1a	Interferon beta-1a 44 mcg subcutaneously 3-times weekly for 24 months. Dose adjustment was done as per Investigator's discretion.
Alemtuzumab	Alemtuzumab 12 mg per day IV infusion on 5 consecutive days at Month 0, followed by alemtuzumab 12 mg per day IV infusion on 3 consecutive days at Month 12.

Baseline Measures

	Interferon Beta-1a	Alemtuzumab	Total
Number of Participants	187	376	563
Age, Continuous [units: years] Mean (Standard Deviation)	33.2 (8.48)	33.0 (8.03)	33.1 (8.18)
Gender, Male/Female [units: participants]			
Female	122	243	365
Male	65	133	198
Time Since First Relapse [units: years] Mean (Standard Deviation)	2.0 (1.32)	2.1 (1.36)	2.1 (1.35)
Number of Relapse Episodes in the Preceding 2 Years [1] [units: participants]			
1 Relapse	3	12	15
2 Relapses	118	215	333
Greater than or equal to 3 Relapses	66	149	215
Expanded Disability Status Scale (EDSS) Score [2] [units: units on a scale]	2.0 (0.79)	2.0 (0.81)	2.0 (0.81)

	Interferon Beta-1a	Alemtuzumab	Total
Mean (Standard Deviation)			

[1] Number of participants with 1, 2 or greater than or equal to 3 relapses are reported.

[2] EDSS is an ordinal scale in half-point increments that quantifies disability in participants with multiple sclerosis (MS). It assesses the 7 functional systems (visual, brainstem, pyramidal, cerebellar, sensory, bowel/bladder and cerebral) as well as ambulation. EDSS total score ranges from 0 (normal neurological examination) to 10 (death due to MS).

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Percentage of Participants With Sustained Accumulation of Disability (SAD)
Measure Description	EDSS is an ordinal scale in half-point increments that quantifies disability in participants with MS. It assesses 7 functional systems (visual, brainstem, pyramidal, cerebellar, sensory, bowel/bladder and cerebral) as well as ambulation. EDSS total score: 0 (normal neurological examination) to 10 (death due to MS). As measured by EDSS score, SAD was defined as increase of at least 1.5 points for participants with Baseline score of 0 and increase of at least 1.0 point for participants with a Baseline score of 1.0 or more; and the increase persisted for at least next 2 scheduled assessments, that is, 6 consecutive months. Onset date of SAD was date of first EDSS assessment that began 6 month consecutive period of SAD. Participants who did not reach SAD endpoint were censored at their last visit. Percentage of participants with SAD, estimated by Kaplan-Meier (KM) method, was reported.
Time Frame	Up to 2 years
Safety Issue?	No

Analysis Population Description

FAS population included all randomized participants who received at least 1 dose of study drug.

Reporting Groups

	Description
Interferon Beta-1a	Interferon beta-1a 44 mcg subcutaneously 3-times weekly for 24 months. Dose adjustment was done as per Investigator's discretion.
Alemtuzumab	Alemtuzumab 12 mg per day IV infusion on 5 consecutive days at Month 0, followed by alemtuzumab 12 mg per day IV infusion on 3 consecutive days at Month 12.

Measured Values

	Interferon Beta-1a	Alemtuzumab
Number of Participants Analyzed	187	376

	Interferon Beta-1a	Alemtuzumab
Percentage of Participants With Sustained Accumulation of Disability (SAD) [units: percentage of participants with SAD] Number (95% Confidence Interval)	11.12 (7.32 to 16.71)	8.00 (5.66 to 11.24)

Statistical Analysis 1 for Percentage of Participants With Sustained Accumulation of Disability (SAD)

Statistical Analysis Overview	Comparison Groups	Interferon Beta-1a, Alemtuzumab
	Comments	Cox proportional hazards (PH) regression model with robust variance estimation using treatment group and geographic region as covariates was used.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.2173
	Comments	Hochberg method was used to adjust for the two co-primary outcomes.
	Method	Other [Cox Proportional Hazards Regression]
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	0.70
	Confidence Interval	(2-Sided) 95% 0.40 to 1.23
	Estimation Comments	[Not specified]

2. Primary Outcome Measure:

Measure Title	Annualized Relapse Rate
Measure Description	Relapse was defined as new neurological symptoms or worsening of previous neurological symptoms with an objective change on neurological examination, attributable to multiple sclerosis that lasted for at least 48 hours, that were present at normal body temperature, and that were preceded by at least 30 days of clinical stability. Annualized relapse rate was estimated through negative binomial regression with robust variance estimation and covariate adjustment for geographic region using observed number of relapses as dependent variable, the log total amount of follow-up from date of first study treatment for each participant as an offset variable, and treatment group and geographic region as model covariates.

Time Frame	Up to 2 years
Safety Issue?	No

Analysis Population Description

FAS population included all randomized participants who received at least 1 dose of study drug.

Reporting Groups

	Description
Interferon Beta-1a	Interferon beta-1a 44 mcg subcutaneously 3-times weekly for 24 months. Dose adjustment was done as per Investigator's discretion.
Alemtuzumab	Alemtuzumab 12 mg per day IV infusion on 5 consecutive days at Month 0, followed by alemtuzumab 12 mg per day IV infusion on 3 consecutive days at Month 12.

Measured Values

	Interferon Beta-1a	Alemtuzumab
Number of Participants Analyzed	187	376
Annualized Relapse Rate [units: relapses per participant per year] Number (95% Confidence Interval)	0.39 (0.29 to 0.53)	0.18 (0.13 to 0.23)

Statistical Analysis 1 for Annualized Relapse Rate

Statistical Analysis Overview	Comparison Groups	Interferon Beta-1a, Alemtuzumab
	Comments	Proportional means regression model with robust variance estimation and covariate adjustment for geographic region was used.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	Hochberg method was used to adjust for the two co-primary outcomes.
	Method	Other [Proportional means regression]
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Other [Rate ratio]

	Estimated Value	0.45
	Confidence Interval	(2-Sided) 95% 0.32 to 0.63
	Estimation Comments	[Not specified]

3. Secondary Outcome Measure:

Measure Title	Percentage of Participants Who Were Relapse Free at Year 2
Measure Description	Participants were considered relapse free at Year 2 if they did not experience a relapse from the date of first study treatment to study completion at 24 months. Percentage of participants who were relapse free at Year 2, estimated using the KM method, was reported.
Time Frame	Year 2
Safety Issue?	No

Analysis Population Description

FAS population included all randomized participants who received at least 1 dose of study drug.

Reporting Groups

	Description
Interferon Beta-1a	Interferon beta-1a 44 mcg subcutaneously 3-times weekly for 24 months. Dose adjustment was done as per Investigator's discretion.
Alemtuzumab	Alemtuzumab 12 mg per day IV infusion on 5 consecutive days at Month 0, followed by alemtuzumab 12 mg per day IV infusion on 3 consecutive days at Month 12.

Measured Values

	Interferon Beta-1a	Alemtuzumab
Number of Participants Analyzed	187	376
Percentage of Participants Who Were Relapse Free at Year 2 [units: percentage of participants] Number (95% Confidence Interval)	58.69 (51.12 to 65.50)	77.59 (72.87 to 81.60)

Statistical Analysis 1 for Percentage of Participants Who Were Relapse Free at Year 2

Statistical Analysis Overview	Comparison Groups	Interferon Beta-1a, Alemtuzumab

	Comments	Cox PH regression model with robust variance estimation, covariate adjustment for geographic region, was used. Secondary endpoints were analyzed sequentially as: Proportion of participants relapse free at Year 2, Change from baseline in EDSS, Percent change from Baseline in magnetic resonance imaging-T2 hyperintense lesion volume at Year 2, Acquisition of disability measured by multiple sclerosis functional composite. Each endpoint could only be formally tested if prior endpoint was significant.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	[Not specified]
	Method	Other [Cox Proportional Hazards Regression]
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	0.45
	Confidence Interval	(2-Sided) 95% 0.33 to 0.61
	Estimation Comments	[Not specified]

4. Secondary Outcome Measure:

Measure Title	Change From Baseline in Expanded Disability Status Scale (EDSS) Score at Year 2
Measure Description	EDSS is an ordinal scale in half-point increments that quantifies disability in participants with MS. It assesses the 7 functional systems (visual, brainstem, pyramidal, cerebellar, sensory, bowel/bladder and cerebral) as well as ambulation. EDSS total score ranges from 0 (normal neurological examination) to 10 (death due to MS). Change was calculated by subtracting Baseline value from value at Year 2.
Time Frame	Baseline, Year 2
Safety Issue?	No

Analysis Population Description

FAS population included all randomized participants who received at least 1 dose of study drug. Here, number of participants analyzed was subset of FAS who had EDSS assessment at both Baseline and end-of-study (Year 2).

Reporting Groups

	Description
Interferon Beta-1a	Interferon beta-1a 44 mcg subcutaneously 3-times weekly for 24 months. Dose adjustment was done as per Investigator's discretion.
Alemtuzumab	Alemtuzumab 12 mg per day IV infusion on 5 consecutive days at Month 0, followed by alemtuzumab 12 mg per day IV infusion on 3 consecutive days at Month 12.

Measured Values

	Interferon Beta-1a	Alemtuzumab
Number of Participants Analyzed	173	366
Change From Baseline in Expanded Disability Status Scale (EDSS) Score at Year 2 [units: units on a scale] Mean (Standard Deviation)	-0.2 (1.05)	-0.2 (0.87)

Statistical Analysis 1 for Change From Baseline in Expanded Disability Status Scale (EDSS) Score at Year 2

Statistical Analysis Overview	Comparison Groups	Interferon Beta-1a, Alemtuzumab
	Comments	The analysis was performed using Wei-Lachin method for non-parametric analysis of repeated measures. Secondary endpoints were analyzed sequentially as: Proportion of participants relapse free at Year 2, Change from baseline in EDSS, Percent change from Baseline in magnetic resonance imaging-T2 hyperintense lesion volume at Year 2, Acquisition of disability measured by multiple sclerosis functional composite. Each endpoint could only be formally tested if prior endpoint was significant.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.4188
	Comments	[Not specified]
	Method	Other [Wei-Lachin]
	Comments	[Not specified]

5. Secondary Outcome Measure:

Measure Title	Change From Baseline in Multiple Sclerosis Functional Composite (MSFC) Score at Year 2

Measure Description	MSFC is a multidimensional measure consisting of quantitative tests of ambulation (Timed 25-Foot Walk), manual dexterity (9-Hole Peg Test; 9HPT), and cognitive function (Paced Auditory Serial Addition Test; PASAT). The MSFC score was calculated as the mean of the Z-scores of the 3 components. A Z-score was calculated by subtracting the mean of the reference population from the test result, then dividing by the standard deviation of the reference population. Higher Z-scores reflected better neurological function and a positive change from Baseline indicates improvement. An increase in score indicated an improvement (Z-score range: -3 to +3). Acquisition of disability was measured by change from Baseline in MSFC score at Year 2.
Time Frame	Baseline, Year 2
Safety Issue?	No

Analysis Population Description

FAS population included all randomized participants who received at least 1 dose of study drug. Here, number of participants analyzed signifies subset of FAS who had MSFC score assessment at Baseline; 'n' signifies participants who had MSFC score assessment at Baseline (for Baseline) and at both Baseline and Year 2 (for change at Year 2).

Reporting Groups

	Description
Interferon Beta-1a	Interferon beta-1a 44 mcg subcutaneously 3-times weekly for 24 months. Dose adjustment was done as per Investigator's discretion.
Alemtuzumab	Alemtuzumab 12 mg per day IV infusion on 5 consecutive days at Month 0, followed by alemtuzumab 12 mg per day IV infusion on 3 consecutive days at Month 12.

Measured Values

	Interferon Beta-1a	Alemtuzumab
Number of Participants Analyzed	186	375
Change From Baseline in Multiple Sclerosis Functional Composite (MSFC) Score at Year 2 [units: Z-score] Mean (Standard Deviation)		
Baseline (n=186, 375)	0.05 (0.629)	-0.02 (0.695)
Change at Year 2 (n=172, 362)	0.07 (0.450)	0.15 (0.516)

Statistical Analysis 1 for Change From Baseline in Multiple Sclerosis Functional Composite (MSFC) Score at Year 2

Statistical Analysis Overview	Comparison Groups	Interferon Beta-1a, Alemtuzumab

	Comments	Change at Year 2: analysis was performed using Wei-Lachin method for non-parametric analysis of repeated measures. Secondary endpoints were analyzed sequentially as: Proportion of participants relapse free at Year 2, Change from baseline in EDSS, Percent change from Baseline in magnetic resonance imaging-T2 hyperintense lesion volume at Year 2, Acquisition of disability measured by MSFC. Each endpoint could only be formally tested if prior endpoint was significant.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0115
	Comments	[Not specified]
	Method	Other [Wei-Lachin]
	Comments	[Not specified]

6. Secondary Outcome Measure:

Measure Title	Percent Change From Baseline in Magnetic Resonance Imaging Time Constant 2 (MRI-T2) Hyperintense Lesion Volume at Year 2
Measure Description	Percent change in MS lesion volume as measured by MRI-T2 scan was calculated from MRI-T2-weighted scans as the following: (lesion volume at 2 years – lesion volume at Baseline)*100/ (lesion volume at Baseline).
Time Frame	Baseline, Year 2
Safety Issue?	No

Analysis Population Description

FAS population included all randomized participants who received at least 1 dose of study drug. Here, number of participants analyzed was subset of FAS who had assessment for T2 volume at both Baseline and end-of-study (Year 2).

Reporting Groups

	Description
Interferon Beta-1a	Interferon beta-1a 44 mcg subcutaneously 3-times weekly for 24 months. Dose adjustment was done as per Investigator's discretion.
Alemtuzumab	Alemtuzumab 12 mg per day IV infusion on 5 consecutive days at Month 0, followed by alemtuzumab 12 mg per day IV infusion on 3 consecutive days at Month 12.

Measured Values

	Interferon Beta-1a	Alemtuzumab
Number of Participants Analyzed	177	364
Percent Change From Baseline in Magnetic Resonance Imaging Time Constant 2 (MRI-T2) Hyperintense Lesion Volume at Year 2 [units: percent change] Mean (Standard Deviation)	-6.68 (32.44)	-10.28 (22.58)

Statistical Analysis 1 for Percent Change From Baseline in Magnetic Resonance Imaging Time Constant 2 (MRI-T2) Hyperintense Lesion Volume at Year 2

Statistical Analysis Overview	Comparison Groups	Interferon Beta-1a, Alemtuzumab
	Comments	Ranked ANCOVA models with covariate adjustment for geographic region and baseline T2 lesion volume was used. Secondary endpoints were analyzed sequentially as: Proportion of participants relapse free at Year 2, Change from baseline in EDSS, Percent change from Baseline in magnetic resonance imaging-T2 hyperintense lesion volume at Year 2, Acquisition of disability measured by multiple sclerosis functional composite. Each endpoint could only be formally tested if prior endpoint was significant.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.3080
	Comments	[Not specified]
	Method	Other [Ranked ANCOVA]
	Comments	[Not specified]

Reported Adverse Events

Time Frame	First dose of study drug up to 2 years
Additional Description	If a participant experienced both a serious and a non-serious event with the same adverse event term, the individual has been included in the numerator ("number of affected participants") of both adverse event tables. The analysis was performed on the safety population, defined as all participants who received any amount of study drug.

Reporting Groups

	Description
Interferon Beta-1a	Interferon beta-1a 44 mcg subcutaneously 3-times weekly for 24 months. Dose adjustment was done as per Investigator's discretion.
Alemtuzumab	Alemtuzumab 12 mg per day IV infusion on 5 consecutive days at Month 0, followed by alemtuzumab 12 mg per day IV infusion on 3 consecutive days at Month 12.

Serious Adverse Events

	Interferon Beta-1a	Alemtuzumab
	Affected/At Risk (%)	Affected/At Risk (%)
Total	27/187 (14.44%)	69/376 (18.35%)
Blood and lymphatic system disorders		
Agranulocytosis [A] *	0/187 (0%)	2/376 (0.53%)
Autoimmune thrombocytopenia [A] *	0/187 (0%)	3/376 (0.8%)
Cardiac disorders		
Atrial fibrillation [A] *	0/187 (0%)	2/376 (0.53%)
Bradycardia [A] *	0/187 (0%)	1/376 (0.27%)
Sinus bradycardia [A] *	0/187 (0%)	1/376 (0.27%)
Sinus tachycardia [A] *	0/187 (0%)	2/376 (0.53%)
Tachycardia [A] *	0/187 (0%)	1/376 (0.27%)
Endocrine disorders		
Basedow's disease [A] *	0/187 (0%)	2/376 (0.53%)
Goitre [A] *	0/187 (0%)	1/376 (0.27%)
Hyperthyroidism [A] *	0/187 (0%)	1/376 (0.27%)
Thyrotoxic crisis [A] *	0/187 (0%)	1/376 (0.27%)
Gastrointestinal disorders		
Colitis [A] *	1/187 (0.53%)	0/376 (0%)
Malocclusion [A] *	1/187 (0.53%)	0/376 (0%)

	Interferon Beta-1a	Alemtuzumab
	Affected/At Risk (%)	Affected/At Risk (%)
Nausea [A] *	0/187 (0%)	1/376 (0.27%)
Oesophagitis [A] *	1/187 (0.53%)	0/376 (0%)
General disorders		
Chest discomfort [A] *	0/187 (0%)	1/376 (0.27%)
Non-cardiac chest pain [A] *	1/187 (0.53%)	0/376 (0%)
Pyrexia [A] *	0/187 (0%)	1/376 (0.27%)
Hepatobiliary disorders		
Hepatitis toxic [A] *	1/187 (0.53%)	0/376 (0%)
Immune system disorders		
Anaphylactic shock [A] *	0/187 (0%)	1/376 (0.27%)
Infections and infestations		
Appendicitis [A] *	1/187 (0.53%)	2/376 (0.53%)
Disseminated tuberculosis [A] *	0/187 (0%)	1/376 (0.27%)
Hepatitis A [A] *	1/187 (0.53%)	0/376 (0%)
Herpes zoster [A] *	0/187 (0%)	1/376 (0.27%)
Meningitis herpes [A] *	0/187 (0%)	1/376 (0.27%)
Postoperative wound infection [A] *	0/187 (0%)	1/376 (0.27%)
Tooth infection [A] *	0/187 (0%)	1/376 (0.27%)
Uterine infection [A] *	0/187 (0%)	1/376 (0.27%)
Injury, poisoning and procedural complications		
Abdominal wound dehiscence [A] *	0/187 (0%)	1/376 (0.27%)
Accidental overdose [A] *	1/187 (0.53%)	0/376 (0%)
Foot fracture [A] *	0/187 (0%)	2/376 (0.53%)

	Interferon Beta-1a	Alemtuzumab
	Affected/At Risk (%)	Affected/At Risk (%)
Forearm fracture [A] *	1/187 (0.53%)	0/376 (0%)
Hand fracture [A] *	1/187 (0.53%)	0/376 (0%)
Humerus fracture [A] *	1/187 (0.53%)	0/376 (0%)
Incorrect dose administered [A] *	0/187 (0%)	2/376 (0.53%)
Joint dislocation [A] *	0/187 (0%)	1/376 (0.27%)
Post procedural haemorrhage [A] *	1/187 (0.53%)	0/376 (0%)
Road traffic accident [A] *	0/187 (0%)	1/376 (0.27%)
Skin laceration [A] *	0/187 (0%)	1/376 (0.27%)
Investigations		
Thyroxine free increased [A] *	0/187 (0%)	1/376 (0.27%)
Tri-iodothyronine free increased [A] *	0/187 (0%)	1/376 (0.27%)
Metabolism and nutrition disorders		
Feeding disorder neonatal [A] *	0/187 (0%)	1/376 (0.27%)
Musculoskeletal and connective tissue disorders		
Myalgia [A] *	0/187 (0%)	1/376 (0.27%)
Osteitis [A] *	1/187 (0.53%)	0/376 (0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Bladder papilloma [A] *	0/187 (0%)	1/376 (0.27%)
Thyroid cancer [A] *	0/187 (0%)	2/376 (0.53%)
Uterine leiomyoma [A] *	0/187 (0%)	1/376 (0.27%)
Nervous system disorders		
Brain stem syndrome [A] *	0/187 (0%)	1/376 (0.27%)
Cerebrovascular insufficiency [A] *	0/187 (0%)	1/376 (0.27%)

	Interferon Beta-1a	Alemtuzumab
	Affected/At Risk (%)	Affected/At Risk (%)
Headache [A] *	0/187 (0%)	2/376 (0.53%)
Hypoxic-ischaemic encephalopathy [A] *	0/187 (0%)	1/376 (0.27%)
Migraine [A] *	0/187 (0%)	1/376 (0.27%)
Multiple sclerosis [A] *	0/187 (0%)	1/376 (0.27%)
Multiple sclerosis relapse [A] *	13/187 (6.95%)	19/376 (5.05%)
Syncope [A] *	0/187 (0%)	2/376 (0.53%)
Psychiatric disorders		
Insomnia [A] *	0/187 (0%)	1/376 (0.27%)
Major depression [A] *	0/187 (0%)	1/376 (0.27%)
Mood altered [A] *	1/187 (0.53%)	0/376 (0%)
Suicide attempt [A] *	0/187 (0%)	1/376 (0.27%)
Renal and urinary disorders		
Nephrolithiasis [A] *	0/187 (0%)	1/376 (0.27%)
Reproductive system and breast disorders		
Menometrorrhagia [A] *	0/187 (0%)	2/376 (0.53%)
Menorrhagia [A] *	0/187 (0%)	1/376 (0.27%)
Ovarian cyst [A] *	0/187 (0%)	1/376 (0.27%)
Ovarian haemorrhage [A] *	1/187 (0.53%)	0/376 (0%)
Uterine polyp [A] *	0/187 (0%)	1/376 (0.27%)
Respiratory, thoracic and mediastinal disorders		
Chronic obstructive pulmonary disease [A] *	1/187 (0.53%)	0/376 (0%)
Pleurisy [A] *	0/187 (0%)	1/376 (0.27%)
Pneumonitis [A] *	0/187 (0%)	1/376 (0.27%)

	Interferon Beta-1a	Alemtuzumab
	Affected/At Risk (%)	Affected/At Risk (%)
Sleep apnoea syndrome [A] *	0/187 (0%)	1/376 (0.27%)
Throat tightness [A] *	0/187 (0%)	1/376 (0.27%)
Skin and subcutaneous tissue disorders		
Angioedema [A] *	0/187 (0%)	1/376 (0.27%)
Increased tendency to bruise [A] *	0/187 (0%)	1/376 (0.27%)
Urticaria [A] *	0/187 (0%)	2/376 (0.53%)
Social circumstances		
Physical assault [A] *	0/187 (0%)	1/376 (0.27%)
Vascular disorders		
Hypotension [A] *	0/187 (0%)	2/376 (0.53%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA 13.1

Other Adverse Events

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

	Interferon Beta-1a	Alemtuzumab
	Affected/At Risk (%)	Affected/At Risk (%)
Total	168/187 (89.84%)	360/376 (95.74%)
Blood and lymphatic system disorders		
Anaemia [A] *	11/187 (5.88%)	8/376 (2.13%)
Leukopenia [A] *	10/187 (5.35%)	11/376 (2.93%)
Lymphopenia [A] *	8/187 (4.28%)	26/376 (6.91%)
Neutropenia [A] *	12/187 (6.42%)	7/376 (1.86%)
Cardiac disorders		
Tachycardia [A] *	3/187 (1.6%)	34/376 (9.04%)

	Interferon Beta-1a	Alemtuzumab
	Affected/At Risk (%)	Affected/At Risk (%)
Gastrointestinal disorders		
Abdominal pain [A] *	5/187 (2.67%)	21/376 (5.59%)
Abdominal pain upper [A] *	0/187 (0%)	22/376 (5.85%)
Diarrhoea [A] *	6/187 (3.21%)	36/376 (9.57%)
Dyspepsia [A] *	8/187 (4.28%)	33/376 (8.78%)
Nausea [A] *	14/187 (7.49%)	65/376 (17.29%)
Vomiting [A] *	4/187 (2.14%)	42/376 (11.17%)
General disorders		
Chest discomfort [A] *	6/187 (3.21%)	25/376 (6.65%)
Chills [A] *	3/187 (1.6%)	38/376 (10.11%)
Fatigue [A] *	23/187 (12.3%)	68/376 (18.09%)
Influenza like illness [A] *	59/187 (31.55%)	19/376 (5.05%)
Injection site erythema [A] *	56/187 (29.95%)	0/376 (0%)
Injection site haematoma [A] *	12/187 (6.42%)	1/376 (0.27%)
Injection site pain [A] *	10/187 (5.35%)	0/376 (0%)
Injection site reaction [A] *	14/187 (7.49%)	0/376 (0%)
Pain [A] *	5/187 (2.67%)	23/376 (6.12%)
Pyrexia [A] *	18/187 (9.63%)	138/376 (36.7%)
Infections and infestations		
Bronchitis [A] *	4/187 (2.14%)	23/376 (6.12%)
Influenza [A] *	11/187 (5.88%)	28/376 (7.45%)
Nasopharyngitis [A] *	25/187 (13.37%)	74/376 (19.68%)

	Interferon Beta-1a	Alemtuzumab
	Affected/At Risk (%)	Affected/At Risk (%)
Oral herpes [A] *	2/187 (1.07%)	40/376 (10.64%)
Rhinitis [A] *	6/187 (3.21%)	20/376 (5.32%)
Sinusitis [A] *	9/187 (4.81%)	30/376 (7.98%)
Upper respiratory tract infection [A] *	25/187 (13.37%)	57/376 (15.16%)
Urinary tract infection [A] *	8/187 (4.28%)	64/376 (17.02%)
Injury, poisoning and procedural complications		
Contusion [A] *	11/187 (5.88%)	38/376 (10.11%)
Investigations		
Alanine aminotransferase increased [A] *	19/187 (10.16%)	2/376 (0.53%)
Aspartate aminotransferase increased [A] *	17/187 (9.09%)	3/376 (0.8%)
B-lymphocyte count decreased [A] *	0/187 (0%)	19/376 (5.05%)
Blood urine present [A] *	6/187 (3.21%)	20/376 (5.32%)
CD4 lymphocytes decreased [A] *	4/187 (2.14%)	26/376 (6.91%)
CD8 lymphocytes decreased [A] *	5/187 (2.67%)	26/376 (6.91%)
T-lymphocyte count decreased [A] *	5/187 (2.67%)	22/376 (5.85%)
Musculoskeletal and connective tissue disorders		
Arthralgia [A] *	10/187 (5.35%)	41/376 (10.9%)
Back pain [A] *	13/187 (6.95%)	48/376 (12.77%)
Muscle spasms [A] *	6/187 (3.21%)	20/376 (5.32%)
Muscular weakness [A] *	11/187 (5.88%)	29/376 (7.71%)
Neck pain [A] *	2/187 (1.07%)	21/376 (5.59%)
Pain in extremity [A] *	15/187 (8.02%)	35/376 (9.31%)
Nervous system disorders		

	Interferon Beta-1a	Alemtuzumab
	Affected/At Risk (%)	Affected/At Risk (%)
Dizziness [A] *	8/187 (4.28%)	33/376 (8.78%)
Dysgeusia [A] *	19/187 (10.16%)	39/376 (10.37%)
Headache [A] *	52/187 (27.81%)	189/376 (50.27%)
Hypoaesthesia [A] *	19/187 (10.16%)	28/376 (7.45%)
Migraine [A] *	11/187 (5.88%)	15/376 (3.99%)
Multiple sclerosis relapse [A] *	64/187 (34.22%)	65/376 (17.29%)
Paraesthesia [A] *	13/187 (6.95%)	32/376 (8.51%)
Psychiatric disorders		
Anxiety [A] *	10/187 (5.35%)	24/376 (6.38%)
Depression [A] *	14/187 (7.49%)	28/376 (7.45%)
Insomnia [A] *	31/187 (16.58%)	56/376 (14.89%)
Reproductive system and breast disorders		
Menorrhagia [A] *	2/187 (1.07%)	24/376 (6.38%)
Respiratory, thoracic and mediastinal disorders		
Cough [A] *	10/187 (5.35%)	39/376 (10.37%)
Dyspnoea [A] *	4/187 (2.14%)	32/376 (8.51%)
Oropharyngeal pain [A] *	11/187 (5.88%)	42/376 (11.17%)
Skin and subcutaneous tissue disorders		
Erythema [A] *	6/187 (3.21%)	20/376 (5.32%)
Pruritus [A] *	3/187 (1.6%)	52/376 (13.83%)
Rash [A] *	9/187 (4.81%)	174/376 (46.28%)
Rash generalised [A] *	2/187 (1.07%)	28/376 (7.45%)
Urticaria [A] *	5/187 (2.67%)	50/376 (13.3%)

	Interferon Beta-1a	Alemtuzumab
	Affected/At Risk (%)	Affected/At Risk (%)
Vascular disorders		
Flushing [A] *	10/187 (5.35%)	44/376 (11.7%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA 13.1

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.

PI can publish after sponsor published, after a defined period of time after study completion, and/or with written sponsor approval. Generally PI gives sponsor a draft 60 days before publication. Sponsor can ask that confidential information be removed, and can further defer publication upon notifying PI that it will file a patent application on inventions contained in the draft.

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