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

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:	NCT00548405

Purpose

The purpose of this study was to establish the efficacy and safety of two different doses of alemtuzumab (Lemtrada™) as a treatment for relapsing-remitting multiple sclerosis (MS), in comparison with subcutaneous interferon beta-1a (Rebif®). The study enrolled participants who had received an adequate trial of disease-modifying therapies but experienced at least 1 relapse during prior treatment, and who met a minimum severity of disease as measured by magnetic resonance imaging (MRI). Participants had monthly laboratory tests and comprehensive testing every 3 months.

Condition	Intervention	Phase
Multiple Sclerosis, Relapsing-Remitting	Biological/Vaccine: Alemtuzumab 12 mg Biological/Vaccine: Alemtuzumab 24 mg 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- and Dose-Blinded Study Comparing Two Annual Cycles of Intravenous Low- and High-Dose Alemtuzumab to Three-Times Weekly Subcutaneous Interferon Beta 1a (Rebif®) in Patients With Relapsing Remitting Multiple Sclerosis Who Have Relapsed On Therapy

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 qualifies 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 the next 2 scheduled assessments, that is, 6 consecutive months. The 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 qualifies 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). 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: 840
Study Start Date: October 2007
Primary Completion Date: September 2011
Study Completion Date: September 2011

Arms	Assigned Interventions
Experimental: Alemtuzumab 12 mg	Biological/Vaccine: Alemtuzumab 12 mg 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
Experimental: Alemtuzumab 24 mg	Biological/Vaccine: Alemtuzumab 24 mg Alemtuzumab 24 mg per day IV infusion on 5 consecutive days at Month 0, followed by alemtuzumab 24 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 received active treatment; there was no placebo. After Amendment 2, the 24 mg alemtuzumab dose was closed to enrollment so newly enrolled participants were randomly assigned to treatment with either 12 mg alemtuzumab or interferon beta-1a in a 2:1 ratio (that is, 2 given 12 mg 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 the CAMMS03409 Extension Study (NCT00930553) for safety and efficacy assessments. Participants who received interferon beta-1a and completed 2 years on study might be eligible to receive alemtuzumab in the Extension Study.

Eligibility

Ages Eligible for Study: 18 Years to 55 Years
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:

- Signed informed consent form (ICF)
- Age 18 to 55 years (inclusive) as of the date the ICF was signed
- Diagnosis of MS per update of McDonald criteria

- Onset of MS symptoms (as determined by a neurologist; could be retrospectively) within 10 years of the date the ICF was signed
- Expanded Disability Status Scale (EDSS) score 0.0 to 5.0 (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
- >=1 MS relapse during treatment with a beta interferon therapy or glatiramer acetate after having been on that therapy for >=6 months within 10 years of the date the ICF was signed
- MRI scan demonstrating white matter lesions attributable to MS and meeting at least 1 of the following criteria, as determined by the neurologist or a radiologist: >=9 time constant 2 (T2) lesions at least 3 millimeter (mm) in any axis; a gadolinium- (Gd-) enhancing lesion at least 3 mm in any axis plus >=1 brain T2 lesions; and a spinal cord lesion consistent with MS plus >=1 brain T2 lesion

Exclusion Criteria:

- Received prior therapy with alemtuzumab
- Current participation in another clinical study or previous participation in CAMMS323 (Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis, CARE-MS I)
- Treatment with natalizumab, methotrexate, azathioprine, or cyclosporine in the past 6 months. Participants who received one of these medications more than 6 months before the date the ICF was signed were eligible for study entry if approval was granted by Genzyme
- Any progressive form of MS
- History of malignancy (except basal skin cell carcinoma)
- CD4 +, CD8 +, CD19 + (that is, absolute CD3 + CD4 + , CD3 + CD8 + , or CD19 + /mm 3) count, absolute neutrophil count less than (<) lower limit of normal (LLN) at screening; if abnormal cell count(s) returned to within normal limits (WNL), eligibility could be reassessed
- 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

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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:

Coles AJ, Twyman CL, Arnold DL, Cohen JA, Confavreux C, Fox EJ, Hartung HP, Havrdova E, Selmaj KW, Weiner HL, Miller T, Fisher E, Sandbrink R, Lake SL, Margolin DH, Oyuela P, Panzara MA, Compston DA; CARE-MS II investigators. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. Lancet. 2012 Nov 24;380(9856):1829-39. doi: 10.1016/S0140-6736(12)61768-1. Epub 2012 Nov 1.

Responsible Party:	Genzyme, a Sanofi Company
Study ID Numbers:	CAMMS32400507 2007-001162-32 [EudraCT Number] CAMMS324, ISRCTN70702834 [Registry ID: ISRCTN] ACTRN12608000426381 [Registry ID: ANZCTR] NTR1469 [Registry ID: The Netherlands National Trial Register] CARE-MS II [NMSS] 2007-001162-32 [EudraCT Number]
Health Authority:	United States: Food and Drug Administration Australia: Department of Health and Ageing Therapeutic Goods Administration Argentina: Administracion Nacional de Medicamentos, Alimentos y Tecnologia Medica Austria: Federal Ministry for Health Family and Youth Belgium: Federal Agency for Medicinal Products and Health Products Brazil: National Health Surveillance Agency Canada: Health Canada Croatia: Agency for Medicinal Product and Medical Devices Czech Republic: State Institute for Drug Control Denmark: Danish Medicines Agency France: Afssaps - Agence française de sécurité sanitaire des produits de santé (Saint-Denis) Germany: Paul-Ehrlich-Institut Israel: Ministry of Health Italy: The Italian Medicines Agency Mexico: Federal Commission for Sanitary Risks Protection Netherlands: Medical Ethics Review Committee (METC) 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 Spain: Spanish Agency of Medicines 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 192 investigational sites between October 10, 2007 and September 15, 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 12 mg	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.
Alemtuzumab 24mg	Alemtuzumab 24 mg per day IV infusion on 5 consecutive days at Month 0, followed by alemtuzumab 24 mg per day IV infusion on 3 consecutive days at Month 12.

Overall Study

	Interferon Beta-1a	Alemtuzumab 12 mg	Alemtuzumab 24mg
Started	231 [1]	436 [1]	173 [1]
Treated	202 [2]	426 [2]	170 [2]
Completed	175	416	164
Not Completed	56	20	9
Adverse Event	6	2	0
Lack of Efficacy	6	0	0
Physician Decision	3	4	1
Pregnancy	1	0	0
Protocol Violation	1	0	0
Withdrawal by Subject	36	12	5
Lost to Follow-up	1	1	2
Death	0	1	1
Sponsor decision	1	0	0
Randomized but not treated	1	0	0

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

Baseline Characteristics

Analysis Population Description

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

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 12 mg	Alemtuzumab 12 mg per day IV infusion on 5 consecutive days at Month 0, followed by alemtuzumab 12 mg per day IV infusion over 4 hours on 3 consecutive days at Month 12.
Alemtuzumab 24mg	Alemtuzumab 24 mg per day IV infusion on 5 consecutive days at Month 0, followed by alemtuzumab 24 mg per day IV infusion over 4 hours on 3 consecutive days at Month 12.

Baseline Measures

	Interferon Beta-1a	Alemtuzumab 12 mg	Alemtuzumab 24mg	Total
Number of Participants	202	426	170	798
Age, Continuous [units: years] Mean (Standard Deviation)	35.8 (8.77)	34.8 (8.36)	35.1 (8.40)	35.1 (8.47)
Gender, Male/Female [units: participants]				
Female	131	281	120	532
Male	71	145	50	266
Time Since First Relapse [units: years] Median (Full Range)	4.1 (0.4 to 10.1)	3.8 (0.2 to 14.4)	3.7 (0.2 to 16.9)	3.8 (0.2 to 16.9)
Number of Relapse Episodes in the Preceding 2 Years [1] [units: participants]				
1 Relapse	7	15	11	33
2 Relapses	109	215	94	418

	Interferon Beta-1a	Alemtuzumab 12 mg	Alemtuzumab 24mg	Total
Greater than or equal to 3 Relapses	86	196	65	347
Expanded Disability Status Scale (EDSS) Score [2] [units: units on a scale] Mean (Standard Deviation)	2.7 (1.21)	2.7 (1.26)	2.7 (1.17)	2.7 (1.22)

[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 qualifies 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 the next 2 scheduled assessments, that is, 6 consecutive months. The 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 as per initial randomization. Analysis was not performed for Alemtuzumab 24 mg as recruitment to this arm was closed early to reduce overall sample size, duration of enrollment period, overall duration of study.

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 12 mg	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 12 mg
Number of Participants Analyzed	202	426
Percentage of Participants With Sustained Accumulation of Disability (SAD) [units: percentage of participants] Number (95% Confidence Interval)	21.13 (15.95 to 27.68)	12.71 (9.89 to 16.27)

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

Statistical Analysis Overview	Comparison Groups	Interferon Beta-1a, Alemtuzumab 12 mg
	Comments	Cox proportional hazards (PH) regression model with robust variance estimation using treatment group and geographic region as covariate was used.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0084
	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	0.58
	Confidence Interval	(2-Sided) 95% 0.38 to 0.87
	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. Analysis was not performed for Alemtuzumab 24 mg as described in outcome measure 1.

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 12 mg	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 12 mg
Number of Participants Analyzed	202	426
Annualized Relapse Rate [units: relapses per participant per year] Number (95% Confidence Interval)	0.52 (0.41 to 0.66)	0.26 (0.21 to 0.33)

Statistical Analysis 1 for Annualized Relapse Rate

Statistical Analysis Overview	Comparison Groups	Interferon Beta-1a, Alemtuzumab 12 mg
	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	0.51
	Confidence Interval	(2-Sided) 95% 0.39 to 0.65
	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. Analysis was not performed for Alemtuzumab 24 mg as described in outcome measure 1.

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 12 mg	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 12 mg
Number of Participants Analyzed	202	426
Percentage of Participants Who Were Relapse Free at Year 2 [units: percentage of participants]	46.70 (39.53 to 53.54)	65.38 (60.65 to 69.70)

	Interferon Beta-1a	Alemtuzumab 12 mg
Number (95% Confidence Interval)		

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

Statistical Analysis Overview	Comparison Groups	Interferon Beta-1a, Alemtuzumab 12 mg
	Comments	Cox PH 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	[Not specified]
	Method	Other [Cox Proportional Hazards Regression]
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	0.53
	Confidence Interval	(2-Sided) 95% 0.41 to 0.69
	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 qualifies 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). 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. Here, number of participants analyzed was subset of FAS who had EDSS assessment at both Baseline and end-of-study (Year 2). Analysis was not performed for Alemtuzumab 24 mg as described in outcome measure 1.

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 12 mg	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 12 mg
Number of Participants Analyzed	174	413
Change From Baseline in Expanded Disability Status Scale (EDSS) Score at Year 2 [units: units on a scale] Mean (Standard Deviation)	0.21 (1.167)	-0.20 (1.084)

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 12 mg
	Comments	The analysis was performed using Wei-Lachin method for non-parametric analysis of repeated measures.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.0001
	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. 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). Analysis was not performed for Alemtuzumab 24 mg as described in outcome measure 1.

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 12 mg	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 12 mg
Number of Participants Analyzed	198	423
Change From Baseline in Multiple Sclerosis Functional Composite (MSFC) Score at Year 2 [units: Z-score] Mean (Standard Deviation)		
Baseline (n=198, 423)	-0.03 (0.791)	0.02 (0.689)
Change at Year 2 (n=169, 399)	-0.04 (0.449)	0.09 (0.358)

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 12 mg
	Comments	Change at Year 2: the analysis was performed using Wei-Lachin method for non-parametric analysis of repeated measures.

	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0022
	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. Here, number of participants analyzed was subset of FAS who had assessment for T2 volume at both Baseline and end-of-study (Year 2). Analysis was not performed for Alemtuzumab 24 mg as described in outcome measure 1.

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 12 mg	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 12 mg
Number of Participants Analyzed	190	412
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)	2.41 (26.48)	-1.12 (24.40)

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 12 mg
	Comments	Ranked ANCOVA models with covariate adjustment for geographic region and Baseline T2 lesion volume was used.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.1371
	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 a serious and a non-serious event with same term, individual was included in numerator of both adverse event tables. Safety population: all participants who received any amount of study drug (as treated). In Alemtuzumab 24 mg arm 9 participants received Alemtuzumab 12 mg, hence were included in Alemtuzumab 12 mg arm.

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 12 mg	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.
Alemtuzumab 24 mg	Alemtuzumab 24 mg per day IV infusion on 5 consecutive days at Month 0, followed by alemtuzumab 24 mg per day IV infusion on 3 consecutive days at Month 12.
Alemtuzumab (Pooled)	Included all participants who received alemtuzumab 12 mg or 24 mg per day IV infusion on 5 consecutive days at Month 0, followed by alemtuzumab 12 mg or 24 mg per day IV infusion on 3 consecutive days at Month 12.

Serious Adverse Events

	Interferon Beta-1a	Alemtuzumab 12 mg	Alemtuzumab 24 mg	Alemtuzumab (Pooled)
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	44/202 (21.78%)	85/435 (19.54%)	30/161 (18.63%)	115/596 (19.3%)
Blood and lymphatic system disorders				
Anaemia [A] *	0/202 (0%)	0/435 (0%)	1/161 (0.62%)	1/596 (0.17%)
Autoimmune thrombocytopenia [A] *	0/202 (0%)	1/435 (0.23%)	2/161 (1.24%)	3/596 (0.5%)
Febrile neutropenia [A] *	0/202 (0%)	0/435 (0%)	1/161 (0.62%)	1/596 (0.17%)
Idiopathic thrombocytopenic purpura [A] *	0/202 (0%)	2/435 (0.46%)	0/161 (0%)	2/596 (0.34%)
Thrombocytopenia [A] *	0/202 (0%)	0/435 (0%)	1/161 (0.62%)	1/596 (0.17%)
Cardiac disorders				
Angina pectoris [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
Coronary artery disease [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
Myocardial infarction [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
Sick sinus syndrome [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
Sinus tachycardia [A] *	0/202 (0%)	0/435 (0%)	1/161 (0.62%)	1/596 (0.17%)
Tachycardia [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
Endocrine disorders				
Goitre [A] *	0/202 (0%)	0/435 (0%)	1/161 (0.62%)	1/596 (0.17%)
Hyperthyroidism [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
Hypothyroidism [A] *	0/202 (0%)	2/435 (0.46%)	1/161 (0.62%)	3/596 (0.5%)
Eye disorders				
Eye pain [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
Retinal pigment epitheliopathy [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
Gastrointestinal disorders				

	Interferon Beta-1a	Alemtuzumab 12 mg	Alemtuzumab 24 mg	Alemtuzumab (Pooled)
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Abdominal pain [A] *	1/202 (0.5%)	2/435 (0.46%)	0/161 (0%)	2/596 (0.34%)
Diarrhoea [A] *	1/202 (0.5%)	0/435 (0%)	0/161 (0%)	0/596 (0%)
Diverticulum [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
Gastritis [A] *	0/202 (0%)	1/435 (0.23%)	1/161 (0.62%)	2/596 (0.34%)
Gastrointestinal necrosis [A] *	0/202 (0%)	0/435 (0%)	1/161 (0.62%)	1/596 (0.17%)
Nausea [A] *	1/202 (0.5%)	1/435 (0.23%)	1/161 (0.62%)	2/596 (0.34%)
Pancreatitis [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
Peptic ulcer perforation [A] *	1/202 (0.5%)	0/435 (0%)	0/161 (0%)	0/596 (0%)
Sigmoiditis [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
Small intestinal obstruction [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
Umbilical hernia [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
Vomiting [A] *	1/202 (0.5%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
General disorders				
Abasia [A] *	0/202 (0%)	0/435 (0%)	1/161 (0.62%)	1/596 (0.17%)
Chest discomfort [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
Chest pain [A] *	0/202 (0%)	2/435 (0.46%)	0/161 (0%)	2/596 (0.34%)
Death [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
Infusion related reaction [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
Non-cardiac chest pain [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
Oedema peripheral [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
Pain [A] *	1/202 (0.5%)	0/435 (0%)	0/161 (0%)	0/596 (0%)
Pyrexia [A] *	0/202 (0%)	2/435 (0.46%)	0/161 (0%)	2/596 (0.34%)

	Interferon Beta-1a	Alemtuzumab 12 mg	Alemtuzumab 24 mg	Alemtuzumab (Pooled)
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Hepatobiliary disorders				
Biliary colic [A] *	1/202 (0.5%)	0/435 (0%)	0/161 (0%)	0/596 (0%)
Cholecystitis [A] *	3/202 (1.49%)	2/435 (0.46%)	0/161 (0%)	2/596 (0.34%)
Cholecystitis acute [A] *	0/202 (0%)	2/435 (0.46%)	0/161 (0%)	2/596 (0.34%)
Hepatitis acute [A] *	1/202 (0.5%)	0/435 (0%)	1/161 (0.62%)	1/596 (0.17%)
Liver disorder [A] *	1/202 (0.5%)	0/435 (0%)	0/161 (0%)	0/596 (0%)
Immune system disorders				
Allergy to arthropod sting [A] *	0/202 (0%)	0/435 (0%)	1/161 (0.62%)	1/596 (0.17%)
Infections and infestations				
Appendicitis [A] *	0/202 (0%)	2/435 (0.46%)	0/161 (0%)	2/596 (0.34%)
Bronchitis [A] *	0/202 (0%)	0/435 (0%)	1/161 (0.62%)	1/596 (0.17%)
Catheter site infection [A] *	1/202 (0.5%)	0/435 (0%)	0/161 (0%)	0/596 (0%)
Diverticulitis [A] *	0/202 (0%)	0/435 (0%)	1/161 (0.62%)	1/596 (0.17%)
Febrile infection [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
Gastroenteritis [A] *	0/202 (0%)	3/435 (0.69%)	1/161 (0.62%)	4/596 (0.67%)
Herpes zoster [A] *	0/202 (0%)	1/435 (0.23%)	2/161 (1.24%)	3/596 (0.5%)
Influenza [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
Injection site abscess [A] *	1/202 (0.5%)	0/435 (0%)	0/161 (0%)	0/596 (0%)
Labyrinthitis [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
Oesophageal candidiasis [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
Pasteurella infection [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
Pneumonia [A] *	0/202 (0%)	4/435 (0.92%)	1/161 (0.62%)	5/596 (0.84%)

	Interferon Beta-1a	Alemtuzumab 12 mg	Alemtuzumab 24 mg	Alemtuzumab (Pooled)
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Pulmonary tuberculosis [A] *	0/202 (0%)	0/435 (0%)	1/161 (0.62%)	1/596 (0.17%)
Pyelonephritis [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
Pyelonephritis chronic [A] *	1/202 (0.5%)	0/435 (0%)	0/161 (0%)	0/596 (0%)
Tooth infection [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
Upper respiratory tract infection [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
Urinary tract infection [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
Injury, poisoning and procedural complications				
Concussion [A] *	0/202 (0%)	0/435 (0%)	1/161 (0.62%)	1/596 (0.17%)
Head injury [A] *	1/202 (0.5%)	0/435 (0%)	0/161 (0%)	0/596 (0%)
Hip fracture [A] *	1/202 (0.5%)	0/435 (0%)	0/161 (0%)	0/596 (0%)
Injury [A] *	1/202 (0.5%)	0/435 (0%)	0/161 (0%)	0/596 (0%)
Jaw fracture [A] *	0/202 (0%)	0/435 (0%)	1/161 (0.62%)	1/596 (0.17%)
Ligament sprain [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
Lip injury [A] *	0/202 (0%)	0/435 (0%)	1/161 (0.62%)	1/596 (0.17%)
Overdose [A] *	1/202 (0.5%)	0/435 (0%)	0/161 (0%)	0/596 (0%)
Radius fracture [A] *	1/202 (0.5%)	0/435 (0%)	0/161 (0%)	0/596 (0%)
Rib fracture [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
Road traffic accident [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
Sternal fracture [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
Subdural haematoma [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
Tendon injury [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
Thoracic vertebral fracture [A] *	1/202 (0.5%)	0/435 (0%)	0/161 (0%)	0/596 (0%)

	Interferon Beta-1a	Alemtuzumab 12 mg	Alemtuzumab 24 mg	Alemtuzumab (Pooled)
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Upper limb fracture [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
Investigations				
Blood creatinine increased [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
Metabolism and nutrition disorders				
Dehydration [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
Musculoskeletal and connective tissue disorders				
Intervertebral disc protrusion [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
Plantar fasciitis [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
Rotator cuff syndrome [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Acute myeloid leukaemia [A] *	1/202 (0.5%)	0/435 (0%)	0/161 (0%)	0/596 (0%)
Basal cell carcinoma [A] *	1/202 (0.5%)	1/435 (0.23%)	1/161 (0.62%)	2/596 (0.34%)
Colon cancer [A] *	0/202 (0%)	0/435 (0%)	1/161 (0.62%)	1/596 (0.17%)
Fibroadenoma of breast [A] *	0/202 (0%)	0/435 (0%)	1/161 (0.62%)	1/596 (0.17%)
Parathyroid tumour benign [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
Thyroid cancer [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
Uterine leiomyoma [A] *	1/202 (0.5%)	0/435 (0%)	0/161 (0%)	0/596 (0%)
Vulval cancer stage 0 [A] *	0/202 (0%)	0/435 (0%)	1/161 (0.62%)	1/596 (0.17%)
Nervous system disorders				
Convulsion [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
Headache [A] *	1/202 (0.5%)	0/435 (0%)	1/161 (0.62%)	1/596 (0.17%)
Intracranial hypotension [A] *	0/202 (0%)	1/435 (0.23%)	1/161 (0.62%)	2/596 (0.34%)
Migraine [A] *	0/202 (0%)	1/435 (0.23%)	1/161 (0.62%)	2/596 (0.34%)

	Interferon Beta-1a	Alemtuzumab 12 mg	Alemtuzumab 24 mg	Alemtuzumab (Pooled)
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Monoparesis [A] *	1/202 (0.5%)	0/435 (0%)	0/161 (0%)	0/596 (0%)
Multiple sclerosis [A] *	0/202 (0%)	0/435 (0%)	1/161 (0.62%)	1/596 (0.17%)
Multiple sclerosis relapse [A] *	25/202 (12.38%)	33/435 (7.59%)	3/161 (1.86%)	36/596 (6.04%)
Post herpetic neuralgia [A] *	0/202 (0%)	0/435 (0%)	1/161 (0.62%)	1/596 (0.17%)
Spinal cord compression [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
Status migrainosus [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
Psychiatric disorders				
Drug dependence [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
Major depression [A] *	0/202 (0%)	0/435 (0%)	1/161 (0.62%)	1/596 (0.17%)
Mania [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
Suicidal ideation [A] *	0/202 (0%)	1/435 (0.23%)	1/161 (0.62%)	2/596 (0.34%)
Suicide attempt [A] *	0/202 (0%)	0/435 (0%)	1/161 (0.62%)	1/596 (0.17%)
Renal and urinary disorders				
Automatic bladder [A] *	1/202 (0.5%)	0/435 (0%)	0/161 (0%)	0/596 (0%)
Renal failure acute [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
Reproductive system and breast disorders				
Cervical dysplasia [A] *	0/202 (0%)	1/435 (0.23%)	1/161 (0.62%)	2/596 (0.34%)
Dysfunctional uterine bleeding [A] *	0/202 (0%)	0/435 (0%)	1/161 (0.62%)	1/596 (0.17%)
Dysmenorrhoea [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
Menorrhagia [A] *	1/202 (0.5%)	0/435 (0%)	0/161 (0%)	0/596 (0%)
Metrorrhagia [A] *	0/202 (0%)	0/435 (0%)	1/161 (0.62%)	1/596 (0.17%)
Uterine prolapse [A] *	1/202 (0.5%)	0/435 (0%)	0/161 (0%)	0/596 (0%)

	Interferon Beta-1a	Alemtuzumab 12 mg	Alemtuzumab 24 mg	Alemtuzumab (Pooled)
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Vulvar dysplasia [A] *	0/202 (0%)	0/435 (0%)	1/161 (0.62%)	1/596 (0.17%)
Respiratory, thoracic and mediastinal disorders				
Cough [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
Dyspnoea [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
Haemoptysis [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
Nasal septum deviation [A] *	1/202 (0.5%)	0/435 (0%)	0/161 (0%)	0/596 (0%)
Oropharyngeal blistering [A] *	0/202 (0%)	0/435 (0%)	1/161 (0.62%)	1/596 (0.17%)
Pleural effusion [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
Pneumonia aspiration [A] *	0/202 (0%)	2/435 (0.46%)	0/161 (0%)	2/596 (0.34%)
Pneumonitis [A] *	0/202 (0%)	0/435 (0%)	1/161 (0.62%)	1/596 (0.17%)
Pulmonary embolism [A] *	1/202 (0.5%)	0/435 (0%)	1/161 (0.62%)	1/596 (0.17%)
Skin and subcutaneous tissue disorders				
Angioedema [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
Rash [A] *	0/202 (0%)	0/435 (0%)	2/161 (1.24%)	2/596 (0.34%)
Urticaria [A] *	0/202 (0%)	2/435 (0.46%)	1/161 (0.62%)	3/596 (0.5%)
Surgical and medical procedures				
Female sterilisation [A] *	0/202 (0%)	0/435 (0%)	1/161 (0.62%)	1/596 (0.17%)
Vascular disorders				
Hypertension [A] *	0/202 (0%)	0/435 (0%)	1/161 (0.62%)	1/596 (0.17%)
Thrombophlebitis [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
Thrombosis [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)
Venous thrombosis limb [A] *	0/202 (0%)	1/435 (0.23%)	0/161 (0%)	1/596 (0.17%)

* 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 12 mg	Alemtuzumab 24 mg	Alemtuzumab (Pooled)
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	189/202 (93.56%)	427/435 (98.16%)	159/161 (98.76%)	586/596 (98.32%)
Blood and lymphatic system disorders				
Lymphopenia [A] *	4/202 (1.98%)	23/435 (5.29%)	9/161 (5.59%)	32/596 (5.37%)
Cardiac disorders				
Tachycardia [A] *	1/202 (0.5%)	27/435 (6.21%)	10/161 (6.21%)	37/596 (6.21%)
Eye disorders				
Vision blurred [A] *	10/202 (4.95%)	21/435 (4.83%)	9/161 (5.59%)	30/596 (5.03%)
Gastrointestinal disorders				
Abdominal pain [A] *	6/202 (2.97%)	23/435 (5.29%)	18/161 (11.18%)	41/596 (6.88%)
Abdominal pain upper [A] *	6/202 (2.97%)	16/435 (3.68%)	11/161 (6.83%)	27/596 (4.53%)
Constipation [A] *	15/202 (7.43%)	19/435 (4.37%)	14/161 (8.7%)	33/596 (5.54%)
Diarrhoea [A] *	17/202 (8.42%)	58/435 (13.33%)	34/161 (21.12%)	92/596 (15.44%)
Dyspepsia [A] *	9/202 (4.46%)	32/435 (7.36%)	19/161 (11.8%)	51/596 (8.56%)
Nausea [A] *	21/202 (10.4%)	105/435 (24.14%)	51/161 (31.68%)	156/596 (26.17%)
Vomiting [A] *	8/202 (3.96%)	39/435 (8.97%)	26/161 (16.15%)	65/596 (10.91%)
General disorders				
Asthenia [A] *	10/202 (4.95%)	22/435 (5.06%)	9/161 (5.59%)	31/596 (5.2%)
Chest discomfort [A] *	1/202 (0.5%)	32/435 (7.36%)	27/161 (16.77%)	59/596 (9.9%)
Chills [A] *	9/202 (4.46%)	35/435 (8.05%)	22/161 (13.66%)	57/596 (9.56%)
Fatigue [A] *	26/202 (12.87%)	81/435 (18.62%)	35/161 (21.74%)	116/596 (19.46%)

	Interferon Beta-1a	Alemtuzumab 12 mg	Alemtuzumab 24 mg	Alemtuzumab (Pooled)
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Influenza like illness [A] *	47/202 (23.27%)	31/435 (7.13%)	13/161 (8.07%)	44/596 (7.38%)
Injection site erythema [A] *	28/202 (13.86%)	0/435 (0%)	0/161 (0%)	0/596 (0%)
Injection site reaction [A] *	13/202 (6.44%)	0/435 (0%)	0/161 (0%)	0/596 (0%)
Oedema peripheral [A] *	4/202 (1.98%)	26/435 (5.98%)	12/161 (7.45%)	38/596 (6.38%)
Pain [A] *	7/202 (3.47%)	35/435 (8.05%)	16/161 (9.94%)	51/596 (8.56%)
Pyrexia [A] *	18/202 (8.91%)	94/435 (21.61%)	47/161 (29.19%)	141/596 (23.66%)
Infections and infestations				
Bronchitis [A] *	10/202 (4.95%)	34/435 (7.82%)	15/161 (9.32%)	49/596 (8.22%)
Gastroenteritis [A] *	5/202 (2.48%)	20/435 (4.6%)	9/161 (5.59%)	29/596 (4.87%)
Gastroenteritis viral [A] *	12/202 (5.94%)	17/435 (3.91%)	8/161 (4.97%)	25/596 (4.19%)
Herpes zoster [A] *	3/202 (1.49%)	24/435 (5.52%)	12/161 (7.45%)	36/596 (6.04%)
Influenza [A] *	11/202 (5.45%)	40/435 (9.2%)	18/161 (11.18%)	58/596 (9.73%)
Nasopharyngitis [A] *	48/202 (23.76%)	128/435 (29.43%)	52/161 (32.3%)	180/596 (30.2%)
Oral herpes [A] *	4/202 (1.98%)	35/435 (8.05%)	9/161 (5.59%)	44/596 (7.38%)
Pharyngitis [A] *	1/202 (0.5%)	19/435 (4.37%)	9/161 (5.59%)	28/596 (4.7%)
Sinusitis [A] *	20/202 (9.9%)	58/435 (13.33%)	20/161 (12.42%)	78/596 (13.09%)
Upper respiratory tract infection [A] *	25/202 (12.38%)	70/435 (16.09%)	34/161 (21.12%)	104/596 (17.45%)
Urinary tract infection [A] *	23/202 (11.39%)	92/435 (21.15%)	37/161 (22.98%)	129/596 (21.64%)
Injury, poisoning and procedural complications				
Contusion [A] *	15/202 (7.43%)	50/435 (11.49%)	30/161 (18.63%)	80/596 (13.42%)
Fall [A] *	11/202 (5.45%)	28/435 (6.44%)	10/161 (6.21%)	38/596 (6.38%)
Investigations				

	Interferon Beta-1a	Alemtuzumab 12 mg	Alemtuzumab 24 mg	Alemtuzumab (Pooled)
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Bacterial test positive [A] *	4/202 (1.98%)	13/435 (2.99%)	9/161 (5.59%)	22/596 (3.69%)
CD4 lymphocytes decreased [A] *	2/202 (0.99%)	23/435 (5.29%)	9/161 (5.59%)	32/596 (5.37%)
CD8 lymphocytes decreased [A] *	4/202 (1.98%)	23/435 (5.29%)	7/161 (4.35%)	30/596 (5.03%)
Lymphocyte count decreased [A] *	5/202 (2.48%)	18/435 (4.14%)	11/161 (6.83%)	29/596 (4.87%)
Platelet count decreased [A] *	12/202 (5.94%)	16/435 (3.68%)	1/161 (0.62%)	17/596 (2.85%)
T-lymphocyte count decreased [A] *	5/202 (2.48%)	16/435 (3.68%)	10/161 (6.21%)	26/596 (4.36%)
Musculoskeletal and connective tissue disorders				
Arthralgia [A] *	25/202 (12.38%)	57/435 (13.1%)	26/161 (16.15%)	83/596 (13.93%)
Back pain [A] *	18/202 (8.91%)	52/435 (11.95%)	30/161 (18.63%)	82/596 (13.76%)
Muscle spasms [A] *	15/202 (7.43%)	28/435 (6.44%)	12/161 (7.45%)	40/596 (6.71%)
Muscular weakness [A] *	14/202 (6.93%)	29/435 (6.67%)	15/161 (9.32%)	44/596 (7.38%)
Myalgia [A] *	13/202 (6.44%)	34/435 (7.82%)	24/161 (14.91%)	58/596 (9.73%)
Pain in extremity [A] *	20/202 (9.9%)	65/435 (14.94%)	26/161 (16.15%)	91/596 (15.27%)
Nervous system disorders				
Dizziness [A] *	11/202 (5.45%)	48/435 (11.03%)	26/161 (16.15%)	74/596 (12.42%)
Dysgeusia [A] *	8/202 (3.96%)	29/435 (6.67%)	14/161 (8.7%)	43/596 (7.21%)
Headache [A] *	35/202 (17.33%)	230/435 (52.87%)	101/161 (62.73%)	331/596 (55.54%)
Hypoaesthesia [A] *	16/202 (7.92%)	35/435 (8.05%)	19/161 (11.8%)	54/596 (9.06%)
Migraine [A] *	11/202 (5.45%)	11/435 (2.53%)	6/161 (3.73%)	17/596 (2.85%)
Multiple sclerosis relapse [A] *	84/202 (41.58%)	119/435 (27.36%)	51/161 (31.68%)	170/596 (28.52%)
Paraesthesia [A] *	20/202 (9.9%)	50/435 (11.49%)	18/161 (11.18%)	68/596 (11.41%)
Tremor [A] *	3/202 (1.49%)	14/435 (3.22%)	10/161 (6.21%)	24/596 (4.03%)

	Interferon Beta-1a	Alemtuzumab 12 mg	Alemtuzumab 24 mg	Alemtuzumab (Pooled)
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Psychiatric disorders				
Anxiety [A] *	14/202 (6.93%)	31/435 (7.13%)	16/161 (9.94%)	47/596 (7.89%)
Depression [A] *	25/202 (12.38%)	29/435 (6.67%)	16/161 (9.94%)	45/596 (7.55%)
Insomnia [A] *	28/202 (13.86%)	69/435 (15.86%)	32/161 (19.88%)	101/596 (16.95%)
Respiratory, thoracic and mediastinal disorders				
Cough [A] *	6/202 (2.97%)	35/435 (8.05%)	22/161 (13.66%)	57/596 (9.56%)
Dyspnoea [A] *	1/202 (0.5%)	37/435 (8.51%)	27/161 (16.77%)	64/596 (10.74%)
Epistaxis [A] *	3/202 (1.49%)	23/435 (5.29%)	7/161 (4.35%)	30/596 (5.03%)
Oropharyngeal pain [A] *	10/202 (4.95%)	47/435 (10.8%)	24/161 (14.91%)	71/596 (11.91%)
Wheezing [A] *	2/202 (0.99%)	4/435 (0.92%)	9/161 (5.59%)	13/596 (2.18%)
Skin and subcutaneous tissue disorders				
Alopecia [A] *	5/202 (2.48%)	12/435 (2.76%)	10/161 (6.21%)	22/596 (3.69%)
Erythema [A] *	3/202 (1.49%)	23/435 (5.29%)	12/161 (7.45%)	35/596 (5.87%)
Pruritus [A] *	5/202 (2.48%)	66/435 (15.17%)	35/161 (21.74%)	101/596 (16.95%)
Rash [A] *	11/202 (5.45%)	193/435 (44.37%)	95/161 (59.01%)	288/596 (48.32%)
Rash generalised [A] *	2/202 (0.99%)	33/435 (7.59%)	16/161 (9.94%)	49/596 (8.22%)
Rash pruritic [A] *	0/202 (0%)	9/435 (2.07%)	11/161 (6.83%)	20/596 (3.36%)
Urticaria [A] *	2/202 (0.99%)	74/435 (17.01%)	42/161 (26.09%)	116/596 (19.46%)
Vascular disorders				
Flushing [A] *	7/202 (3.47%)	34/435 (7.82%)	16/161 (9.94%)	50/596 (8.39%)

* Indicates events were collected by non-systematic methods.

A Term from vocabulary, MedDRA 13.1

Limitations and Caveats

Efficacy analysis was not performed for Alemtuzumab 24 mg as recruitment to this arm was closed early to reduce overall sample size, duration of enrollment period, overall duration of study.

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 can 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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