Clinical trial results:
A long-term follow-up study for Multiple Sclerosis patients who have completed the alemtuzumab Extension Study (CAMMS03409)

Summary

EudraCT number	2013-003884-71
Trial protocol	BE NL CZ ES DE IT DK HR
Global end of trial date	15 July 2020

Results information

Result version number	v1 (current)
This version publication date	26 July 2021
First version publication date	26 July 2021

Trial information

Trial identification

Sponsor protocol code	LPS13649

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02255656
WHO universal trial number (UTN)	U1111-1148-2987

Notes:

Sponsors

Sponsor organisation name	Genzyme Corporation, a Sanofi company
Sponsor organisation address	50 Binney St., Cambridge, Massachusetts, United States, 02142
Public contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 August 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 July 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate long-term safety of alemtuzumab.

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency. Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 January 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 7
Country: Number of subjects enrolled	Australia: 43
Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	Poland: 53
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	Sweden: 5
Country: Number of subjects enrolled	United Kingdom: 81
Country: Number of subjects enrolled	Croatia: 111
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Czechia: 27
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	Germany: 38
Country: Number of subjects enrolled	Italy: 12
Country: Number of subjects enrolled	Brazil: 29
Country: Number of subjects enrolled	Israel: 5
Country: Number of subjects enrolled	Russian Federation: 136
Country: Number of subjects enrolled	Ukraine: 57
Country: Number of subjects enrolled	United States: 347

Country: Number of subjects enrolled	Canada: 29
Country: Number of subjects enrolled	Mexico: 13
Country: Number of subjects enrolled	Serbia: 49
Worldwide total number of subjects	1062
EEA total number of subjects	266

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	1061
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 142 study centres in 21 countries. A total of 1062 subjects were screened between 7 January 2015 and 28 June 2016 and were enrolled in current study (LPS13649 [TOPAZ]).

Pre-assignment

Screening details:

Subgroup analysis (DAT subgroup and IAT subgroup) performed only for end-points and safety analysis. Subjects rolled over from CAMMS223 (NCT00050778) to CAMMS03409 (NCT00930553), then subsequently enrolled and took 24 mg alemtuzumab in CAMMS324 (NCT00548405) study, were not considered as part of DAT/IAT subgroup and included in overall group.

Period 1

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

Arms

Arm title	Alemtuzumab

Arm description:

All Subjects who completed the study CAMMS03409 (extension study of CAMMS223 [NCT00050778], CAMMS323 [NCT00530348], or CAMMS324 [NCT00548405]) and received alemtuzumab within 48 months prior to enrollment were included in this LPS13649 study. Subjects received alemtuzumab, intravenous infusion of 12 milligrams per day (mg/day) for 3 consecutive days, at the study investigators' discretion; and at least 12 months after the prior treatment course in the current study (LPS13649).

Arm type	Experimental
Investigational medicinal product name	Alemtuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received alemtuzumab, intravenous infusion of 12 mg/day for 3 consecutive days, at the study investigators' discretion; and at least 12 months after the prior treatment course in the current study (LPS13649).

Number of subjects in period 1	Alemtuzumab
Started	1062
Completed	592
Not completed	470
Adverse Event	11
Due to Coronavirus Disease (Covid-19)	300
Poor compliance to protocol	3
Unspecified	126
Lost to follow-up	30

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description:

All Subjects who completed the study CAMM03409 (extension study of CAMMS223 [NCT00050778],CAMMS323 [NCT00530348], or CAMMS324 [NCT00548405]) and received alemtuzumab within 48 months prior to enrollment were included in this LPS13649 study. Subjects received alemtuzumab, intravenous infusion of 12 mg/day for 3 consecutive days, at the study investigators' discretion; and at least 12 months after the prior treatment course in the current study

Reporting group values	Overall Study	Total	
Number of subjects	1062	1062	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	41.2		
standard deviation	± 8.6	-	
Gender categorical Units: Subjects			
Female	686	686	
Male	376	376	
Race/Ethnicity Units: Subjects			
White	988	988	
Black or African American	34	34	
Asian	5	5	
American Indian or Alaska native	6	6	
Other	29	29	

End points

End points reporting groups

Reporting group title	Alemtuzumab

Reporting group description:

All Subjects who completed the study CAMMS03409 (extension study of CAMMS223 [NCT00050778], CAMMS323 [NCT00530348], or CAMMS324 [NCT00548405]) and received alemtuzumab within 48 months prior to enrollment were included in this LPS13649 study. Subjects received alemtuzumab, intravenous infusion of 12 milligrams per day (mg/day) for 3 consecutive days, at the study investigators' discretion; and at least 12 months after the prior treatment course in the current study (LPS13649).

Subject analysis set title	Delayed Alemtuzumab Treatment (DAT)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects from the subcutaneous interferon beta-1a (SC IFNB1a) treatment arms of studies CAMMS323 and CAMMS324, who received their initial 2 treatment courses of alemtuzumab during the CAMMS03409 extension study were included in the DAT subgroup of the current study (LPS13649). Subjects received alemtuzumab intravenous infusion of 12 mg/day for 3 consecutive days, at the study investigators' discretion; and at least 12 months after the prior treatment course in the current study (LPS13649).

Subject analysis set title	Initial Alemtuzumab Treatment (IAT)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects from the 12 mg/day alemtuzumab treatment arms of the studies CAMMS323 and CAMMS324 (who were subsequently enrolled in CAMMS03409 extension study and then entered in this study LPS13649) were included in the IAT subgroup of the current study (LPS13649). Subjects received alemtuzumab intravenous infusion of 12 mg/day for 3 consecutive days, at the study investigators' discretion; and at least 12 months after the prior treatment course in the current study (LPS13649).

Primary: Number of Subjects With Treatment-emergent Adverse Events (TEAEs), and Treatment-emergent Serious Adverse Events (TESAEs)

End point title	Number of Subjects With Treatment-emergent Adverse Events (TEAEs), and Treatment-emergent Serious Adverse Events (TESAEs)[1]

End point description:

An Adverse Event (AE) was any untoward medical occurrence in a subject administered a pharmaceutical product and which did not necessarily had to have causal relationship with treatment. TEAEs were defined as AEs that developed/worsened during the 'treatment period (time from Baseline until the end of the study LPS13649 [i.e. up to a maximum of 5.6 years]). Serious AE (SAE) was any untoward medical occurrence that at any dose: resulted in death, was life-threatening, required inpatient hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect, was a medically important event. Analysis was performed on safety analysis set that included all subjects who signed the informed consent form (ICF). As pre-specified, data collection and analysis for this endpoint was done on the overall population along with the 2 subgroups (DAT and IAT).

End point type	Primary

End point timeframe:

From Baseline until the end of the study (up to a maximum duration of 5.6 years)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As the endpoint was descriptive in nature, no statistical analysis was provided.

End point values	Alemtuzumab	Delayed Alemtuzumab Treatment (DAT)	Initial Alemtuzumab Treatment (IAT)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	1062	241	598	
Units: subjects				
Any TEAE	879	204	500	
Any TESAE	237	55	133	
Any TEAE leading to death	11	0	10	
Any TEAE led permanent treatment discontinuation	2	0	2	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Infusion-Associated Reactions (IAR)

End point title	Number of Subjects With Infusion-Associated Reactions (IAR)[2]

End point description:

IAR was defined as any AE occurring during and within 24 hours of alemtuzumab infusion. Analysis was performed on re-treated population that included all subjects who have signed the ICF and who had received study drug in the current study LPS13649. Here, 'number of subject analysed' = subjects evaluable for this endpoint. As pre-specified, data collection and analysis for this endpoint was done on the overall population along with the 2 subgroups (DAT and IAT).

End point type	Primary

End point timeframe:

Within 24 hours of any alemtuzumab infusion

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As the endpoint was descriptive in nature, no statistical analysis was provided.

End point values	Alemtuzumab	Delayed Alemtuzumab Treatment (DAT)	Initial Alemtuzumab Treatment (IAT)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	294	83	164	
Units: subjects	164	48	89	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Adverse Events of Special Interest (AESI)

End point title	Number of Subjects With Adverse Events of Special Interest (AESI)[3]

End point description:

AESI included the following: hypersensitivity or anaphylaxis; pregnancy of a woman entered in the study; symptomatic overdose (serious or non-serious) with investigational medicinal product (IMP);

increase in alanine transaminase (ALT); autoimmune mediated conditions; hemophagocytic lymphohistiocytosis; progressive multifocal leukoencephalopathy; temporally associated AEs; serious infections; malignancy; and pneumonitis. Analysis was performed on safety population. As pre-specified, data collection and analysis for this endpoint was done on the overall population along with the 2 subgroups (DAT and IAT).

End point type	Primary

End point timeframe:

From Baseline until the end of the study (up to a maximum duration of 5.6 years)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As the endpoint was descriptive in nature, no statistical analysis was provided.

End point values	Alemtuzumab	Delayed Alemtuzumab Treatment (DAT)	Initial Alemtuzumab Treatment (IAT)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	1062	241	598	
Units: subjects				
Hypersensitivity or anaphylaxis	44	12	25	
Pregnancy of a woman entered in the study	70	17	42	
Symptomatic overdose (serious/non-serious)with IMP	0	0	0	
Increase in ALT	1	0	0	
Autoimmune mediated conditions	100	27	66	
Hemophagocytic lymphohistiocytosis	0	0	0	
Progressive multifocal leukoencephalopathy	0	0	0	
Temporally associated AEs	9	2	4	
Serious infections	60	10	35	
Malignancy	27	6	15	
Pneumonitis	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Potentially Clinically Significant Laboratory Abnormalities

End point title	Number of Subjects With Potentially Clinically Significant Laboratory Abnormalities[4]

End point description:

Criteria for potentially clinically significant laboratory abnormalities included: • Hemoglobin (Hb): less than or equal to (<=)115 grams per liter (g/L)(Male [M]), <= 95 g/L (Female[F]); greater than or equal to (>=)185 g/L (M), >= 165 g/L (F); Decrease From Baseline (DFB) >= 20 g/L. • Hematocrit: <= 0.37 volume/volume (v/v) (M); <= 0.32 v/v (F); >= 0.55 v/v (M); >= 0.5 v/v (F). • RBCs: >=6 *10^12/L. •Platelets: <100 *10^9/L; >=700 *10^9/L. Analysis was performed on all subjects who have signed the ICF; and received study drug in the TOPAZ study; or in studies CAMMS223,CAMMS323,CAMMS324 or CAMMS03409, and did not complete 48 months of follow-up at the screening visit in the TOPAZ study. Here, 'number of subjects analysed'=subjects evaluable for this endpoint and 'n' = subjects with available data for each specified category. As pre-specified, data collection and analysis for this endpoint was done on the overall population along with the 2 subgroups

End point type	Primary

End point timeframe:

From Baseline until the end of the study (up to a maximum duration of 5.6 years)

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As the endpoint was descriptive in nature, no statistical analysis was provided.

End point values	Alemtuzumab	Delayed Alemtuzumab Treatment (DAT)	Initial Alemtuzumab Treatment (IAT)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	619	214	316	
Units: subjects				
Hb:<=115 g/L, <=95 g/L(n=619,214,316)	43	11	28	
Hb: >=185 g/L, >=165 g/L(n=619,214,316)	12	2	6	
Hb: DFB >=20 g/L (n=580,206,293)	98	32	50	
Hematocrit: <= 0.37 v/v; <=0.32 v/v(n=617,213,315)	70	20	42	
Hematocrit: >=0.55 v/v; >=0.5 v/v(n=617,213,315)	26	6	14	
RBCs: >=6 *10^12/L(n=618,214,315)	21	8	7	
Platelets: <100 *10^9/L(n=615,212,314)	25	5	16	
Platelets: >=700 *10^9/L(n=615,212,314)	1	1	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Annualised Relapse Rate

End point title	Annualised Relapse Rate

End point description:

Relapse was defined as new neurological symptoms or worsening of previous neurological symptoms with an objective change on neurological examination. Annualised relapse rate was obtained from the total number of confirmed relapses that occurred during the treatment follow up time of all subjects divided by the total years of follow-up for all subjects. The annualised relapse rate was estimated using a negative binomial model with robust variance estimation. Analysis was performed on efficacy population which included all enrolled subjects who received study drug in studies CAMMS223, CAMMS323, CAMMS324 or CAMMS03409. As pre-specified, data collection and analysis for this endpoint was done only on the 2 subgroups (DAT and IAT).

End point type	Secondary

End point timeframe:

Up to a maximum duration of 5.6 years

End point values	Delayed Alemtuzumab Treatment (DAT)	Initial Alemtuzumab Treatment (IAT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	241	598		
Units: relapses per subject per year				
number (confidence interval 95%)	0.1994 (0.1710 to 0.2325)	0.1608 (0.1418 to 0.1823)		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects Who Were Relapse Free

End point title	Proportion of Subjects Who Were Relapse Free

End point description:

Relapse was defined as new neurological symptoms or worsening of previous neurological symptoms with an objective change on neurological examination. The proportion of subjects who were relapse free (without event) were estimated using the Kaplan-Meier method. Analysis was performed on efficacy population. As pre-specified, data collection and analysis for this endpoint was done only on the 2 subgroups (DAT and IAT).

End point type	Secondary

End point timeframe:

Up to a maximum duration of 5.6 years

End point values	Delayed Alemtuzumab Treatment (DAT)	Initial Alemtuzumab Treatment (IAT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	241	598		
Units: proportion of subjects				
number (confidence interval 95%)	29.59 (23.73 to 35.65)	36.86 (32.96 to 40.76)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Expanded Disability Status Scale (EDSS) Score at Month 6, 12, 18, 24, 30, 36,42, 48, 54 and 60

End point title	Change From Baseline in Expanded Disability Status Scale (EDSS) Score at Month 6, 12, 18, 24, 30, 36,42, 48, 54 and 60

End point description:

EDSS is an ordinal scale in half-point increments that qualifies disability in subjects with multiple sclerosis (MS). It consists of 8 ordinal rating scales assessing seven functional systems (pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral, and other). EDSS total score ranges

from 0 (normal neurological examination) to 10 (death due to MS), where higher scores indicated worst outcomes. Analysis was performed on efficacy population. Here, 'n' = subjects with available data for each specified category. As pre-specified, data collection and analysis for this endpoint was done only on the 2 subgroups (DAT and IAT).

End point type	Secondary

End point timeframe:

Baseline (Month 0 of LPS13649), Month 6, 12, 18, 24, 30, 36,42, 48, 54 and 60

End point values	Delayed Alemtuzumab Treatment (DAT)	Initial Alemtuzumab Treatment (IAT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	241	598		
Units: score on a scale				
least squares mean (standard error)				
Month 6 (n=237,583)	0.21 (± 0.092)	0.03 (± 0.065)		
Month 12 (n=234,580)	0.27 (± 0.093)	0.08 (± 0.065)		
Month 18 (n=226,562)	0.29 (± 0.096)	0.10 (± 0.067)		
Month 24 (n=227,559)	0.28 (± 0.102)	0.15 (± 0.070)		
Month 30 (n=225,547)	0.34 (± 0.102)	0.16 (± 0.071)		
Month 36 (n=219,545)	0.38 (± 0.103)	0.18 (± 0.071)		
Month 42 (n=217,515)	0.37 (± 0.103)	0.24 (± 0.071)		
Month 48 (n=204,468)	0.46 (± 0.104)	0.27 (± 0.072)		
Month 54 (n=168,346)	0.51 (± 0.106)	0.30 (± 0.074)		
Month 60 (n=55,125)	0.43 (± 0.129)	0.32 (± 0.088)		

Statistical analyses

No statistical analyses for this end point

Secondary: Brain Magnetic Resonance Imaging (MRI) Assessment: Number of Gadolinium Enhancing (Gd-enhancing) Lesions Per MRI Scan

End point title	Brain Magnetic Resonance Imaging (MRI) Assessment: Number of Gadolinium Enhancing (Gd-enhancing) Lesions Per MRI Scan

End point description:

Number of Gd-enhancing lesions per scan was defined as the total number of Gd-enhancing lesions that occurred during the treatment period divided by the total number of scans performed during the treatment period. The adjusted cumulative count of lesions was estimated by a repeated negative binomial regression with generalised estimating equation (GEE) adjusted for analysis groups and geographic region as covariates. Analysis was performed on efficacy population. As pre-specified, data collection and analysis for this endpoint was done only on the 2 subgroups (DAT and IAT).

End point type	Secondary

End point timeframe:

Up to a maximum duration of 5.6 years

End point values	Delayed Alemtuzumab Treatment (DAT)	Initial Alemtuzumab Treatment (IAT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	241	598		
Units: lesions per scan				
number (confidence interval 95%)	1.307 (0.880 to 1.941)	1.558 (1.153 to 2.105)		

Statistical analyses

No statistical analyses for this end point

Secondary: Brain Magnetic Resonance Imaging (MRI) Assessment: Number of New or Enlarged T2 Lesions Per MRI Scan

End point title	Brain Magnetic Resonance Imaging (MRI) Assessment: Number of New or Enlarged T2 Lesions Per MRI Scan

End point description:

Number of new or enlarged T2 lesions per scan was defined as the total number of new or enlarged T2 lesion that occurred during treatment period divided by the total number of scans performed during treatment period. The adjusted cumulative count of lesions was estimated by a repeated negative binomial regression with GEE adjusted for analysis groups and geographic region as covariates. Analysis was performed on efficacy population. As pre-specified, data collection and analysis for this endpoint was done only on the 2 subgroups (DAT and IAT).

End point type	Secondary

End point timeframe:

Up to a maximum duration of 5.6 years

End point values	Delayed Alemtuzumab Treatment (DAT)	Initial Alemtuzumab Treatment (IAT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	241	598		
Units: lesions per scan				
number (confidence interval 95%)	8.033 (6.001 to 10.753)	9.564 (7.656 to 11.946)		

Statistical analyses

No statistical analyses for this end point

Secondary: Brain Magnetic Resonance Imaging (MRI) Assessment: Number of New T1 (and New Hypointense T1) Lesions Per MRI Scan

End point title	Brain Magnetic Resonance Imaging (MRI) Assessment: Number of New T1 (and New Hypointense T1) Lesions Per MRI Scan

End point description:

Number of new T1 lesions per scan was defined as the total number of new T1 lesion (and New

Hypointense T1) that occurred during treatment period divided by the total number of scans performed during treatment period. The adjusted cumulative count of lesions was estimated by a repeated negative binomial regression with GEE adjusted for analysis groups and geographic region as covariates. As pre-specified, data collection and analysis for this endpoint was done only on the 2 subgroups (DAT and IAT).

End point type	Secondary

End point timeframe:

Up to a maximum duration of 5.6 years

End point values	Delayed Alemtuzumab Treatment (DAT)	Initial Alemtuzumab Treatment (IAT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	241	598		
Units: lesions per scan				
number (confidence interval 95%)	1.719 (1.141 to 2.589)	1.908 (1.386 to 2.628)		

Statistical analyses

No statistical analyses for this end point

Secondary: Brain Magnetic Resonance Imaging (MRI) Assessment: Percent Change From Baseline in Volume of T1 Lesions at Months 12, 24, 36, 48 and 60

End point title	Brain Magnetic Resonance Imaging (MRI) Assessment: Percent Change From Baseline in Volume of T1 Lesions at Months 12, 24, 36, 48 and 60

End point description:

The total lesion volume (T1 lesions) was measured by MRI scan. Analysis was preformed on efficacy population. Here, 'n' = subjects with available data for each specified category. As pre-specified, data collection and analysis for this endpoint was done only on the 2 subgroups (DAT and IAT).

End point type	Secondary

End point timeframe:

Baseline (Month 0 of LPS13649), Month 12, Month 24, Month 36, Month 48 and Month 60

End point values	Delayed Alemtuzumab Treatment (DAT)	Initial Alemtuzumab Treatment (IAT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	241	598		
Units: percent change				
arithmetic mean (standard deviation)				
Month 12 (n=203,501)	141.71 (± 449.79)	64.73 (± 241.92)		
Month 24 (n=202,489)	130.73 (± 398.65)	67.48 (± 262.64)		

Month 36 (n=194,478)	145.57 (± 404.35)	104.41 (± 524.62)		
Month 48 (n=185,421)	163.30 (± 461.38)	76.90 (± 312.05)		
Month 60 (n=60,116)	202.47 (± 499.46)	93.61 (± 260.51)		

Statistical analyses

No statistical analyses for this end point

Secondary: Brain Magnetic Resonance Imaging (MRI) Assessment: Percent Change From Baseline in Volume of T2 Lesions at Months 12, 24, 36, 48 and 60

End point title	Brain Magnetic Resonance Imaging (MRI) Assessment: Percent Change From Baseline in Volume of T2 Lesions at Months 12, 24, 36, 48 and 60

End point description:

The total lesion volume (T2 lesions) was measured by MRI scan. Analysis was performed on efficacy population. Here, 'n' = subjects with available data for each specified category. As pre-specified, data collection and analysis for this endpoint was done only on the 2 subgroups (DAT and IAT).

End point type	Secondary

End point timeframe:

Baseline (Month 0 of LPS13649), Month 12, Month 24, Month 36, Month 48 and Month 60

End point values	Delayed Alemtuzumab Treatment (DAT)	Initial Alemtuzumab Treatment (IAT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	241	598		
Units: percent change				
arithmetic mean (standard deviation)				
Month 12 (n=226,558)	21.44 (± 132.04)	9.09 (± 62.52)		
Month 24 (n=224,542)	17.53 (± 76.73)	13.89 (± 62.45)		
Month 36 (n=216,529)	24.24 (± 94.85)	22.02 (± 111.95)		
Month 48 (n=204,462)	21.98 (± 80.06)	19.46 (± 70.72)		
Month 60 (n=67,128)	32.03 (± 136.68)	17.95 (± 75.47)		

Statistical analyses

No statistical analyses for this end point

Secondary: Brain Magnetic Resonance Imaging (MRI) Assessment: Percent Change From Baseline in Brain Parenchymal Fraction (BPF) at Month 12, 24, 36, 48 and 60

End point title	Brain Magnetic Resonance Imaging (MRI) Assessment: Percent Change From Baseline in Brain Parenchymal Fraction (BPF) at Month 12, 24, 36, 48 and 60

End point description:

The brain parenchymal fraction was measured by MRI scan. Analysis was performed on efficacy population. Here, 'n' = subjects with available data for each specified category. As pre-specified, data collection and analysis for this endpoint was done only on the 2 subgroups (DAT and IAT).

End point type	Secondary

End point timeframe:

Baseline (Month 0 of LPS13649), Month 12, Month 24, Month 36, Month 48 and Month 60

End point values	Delayed Alemtuzumab Treatment (DAT)	Initial Alemtuzumab Treatment (IAT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	241	598		
Units: percent change				
arithmetic mean (standard deviation)				
Month 12 (n=221,549)	-1.65 (± 1.59)	-1.49 (± 1.55)		
Month 24 (n=220,534)	-1.77 (± 1.56)	-1.68 (± 1.64)		
Month 36 (n=215,524)	-1.92 (± 1.56)	-1.84 (± 1.71)		
Month 48 (n=203,459)	-2.02 (± 1.58)	-2.07 (± 1.78)		
Month 60 (n=66,129)	-2.11 (± 1.67)	-2.37 (± 1.65)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Self-reported Quality of Life (QoL) as Assessed by the Medical Outcome Study (MOS) 36- Item Short-Form Health Survey (SF-36) Physical Component Summary (PCS) and Mental Component Summary (MCS) Scores at Month 12, 24, 36, 48 and 60

End point title	Change From Baseline in Self-reported Quality of Life (QoL) as Assessed by the Medical Outcome Study (MOS) 36- Item Short-Form Health Survey (SF-36) Physical Component Summary (PCS) and Mental Component Summary (MCS) Scores at Month 12, 24, 36, 48 and 60

End point description:

The MOS SF-36 is an extensively validated and widely used measure of QoL that assesses subjects' perceptions of health status and its impact on their lives. It consisted of 36 items organised into 8 scales (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health). Two summary measures of physical and mental health, the PCS and MCS, respectively, were derived from scale aggregates, and were reported in this endpoint. The score range for each of these 2 summary scores was from 0 (worst) to 100 (best), higher scores indicated better QoL. Analysis was performed on efficacy population. Here, 'n' = subjects with available data for each specified category. As pre-specified, data collection and analysis for this endpoint was done only on the 2 subgroups (DAT and IAT).

End point type	Secondary

End point timeframe:

Baseline (Month 0 of LPS13649), Month 12, Month 24, Month 36, Month 48 and Month 60

End point values	Delayed Alemtuzumab Treatment (DAT)	Initial Alemtuzumab Treatment (IAT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	241	598		
Units: score on a scale				
arithmetic mean (standard deviation)				
PCS: Month 12 (n=228,559)	0.54 (± 9.38)	0.88 (± 8.72)		
PCS: Month 24 (n=216,545)	0.20 (± 9.25)	0.59 (± 9.10)		
PCS: Month 36 (n=212,534)	0.08 (± 9.88)	1.12 (± 9.18)		
PCS: Month 48 (n=199,466)	-0.52 (± 10.15)	0.68 (± 9.57)		
PCS: Month 60 (n=80,176)	-0.23 (± 8.85)	1.28 (± 8.88)		
MCS: Month 12 (n=228,559)	2.21 (± 12.29)	0.89 (± 11.24)		
MCS: Month 24 (n=216,545)	1.21 (± 12.23)	1.11 (± 11.93)		
MCS: Month 36 (n=212,534)	1.55 (± 12.23)	0.94 (± 11.88)		
MCS: Month 48 (n=199,466)	1.14 (± 12.93)	0.35 (± 12.38)		
MCS: Month 60 (n=80,176)	0.94 (± 14.01)	0.45 (± 11.39)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Functional Assessment of Multiple Sclerosis (FAMS) Score at Month 12, 24, 36, 48 and 60

End point title	Change From Baseline in Functional Assessment of Multiple Sclerosis (FAMS) Score at Month 12, 24, 36, 48 and 60

End point description:

The FAMS is a self-reported multidimensional index comprising a total of 58 items on 7 subscales: mobility (7 items); symptoms (7 items); emotional well-being (7 items); general contentment (7 items); thinking and fatigue (9 items); family/social well-being (7 items); and additional concerns (14 items, these are not scored). Each item (except those for "additional concerns") was rated on a 5-point scale of 0 (lower quality of life) to 4 (higher quality of life). Total FAMS score was the sum of 44 scored items, which ranged from 0 (poor) to 176 (best), with higher numbers reflecting a higher quality of life. Analysis was performed on efficacy population. Here, 'n' = subjects with available data for each specified category. As pre-specified, data collection and analysis for this endpoint was done only on the 2 subgroups (DAT and IAT).

End point type	Secondary

End point timeframe:

Baseline (Month 0 of LPS13649), Month 12, Month 24, Month 36, Month 48 and Month 60

End point values	Delayed Alemtuzumab Treatment (DAT)	Initial Alemtuzumab Treatment (IAT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	241	598		
Units: score on a scale				
arithmetic mean (standard deviation)				
Month 12 (n=230,573)	1.05 (± 29.68)	2.83 (± 27.07)		
Month 24 (n=222,551)	-0.45 (± 30.30)	2.73 (± 28.62)		
Month 36 (n=214,532)	0.82 (± 30.52)	2.70 (± 28.94)		
Month 48 (n=202,472)	-3.73 (± 31.46)	1.16 (± 29.38)		
Month 60 (n=81,181)	-0.36 (± 31.25)	2.74 (± 26.61)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Quality of Life -5 Dimension (EQ-5D) Score: Utility Scores at Month 12, 24, 36, 48 and 60

End point title	Change From Baseline in European Quality of Life -5 Dimension (EQ-5D) Score: Utility Scores at Month 12, 24, 36, 48 and 60

End point description:

The EQ-5D is a generic, standardised instrument that provides a simple, descriptive profile and a single index value for health status used in the clinical and economic evaluation of health care as well as in population health surveys. The EQ-5D comprises 5 dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension measured on 3 levels: some, moderate, and extreme problems. The 5 dimensional 3-level systems was converted into single index utility score ranges from 0 to 100, where 100=best health state; and 0=worst health state; higher scores indicated better outcome. Analysis was performed on efficacy population. Here, 'n' = subjects with available data for each specified category. As pre-specified, data collection and analysis for this endpoint was done only on the 2 subgroups (DAT and IAT).

End point type	Secondary

End point timeframe:

Baseline (Month 0 of LPS13649), Month 12, Month 24, Month 36, Month 48 and Month 60

End point values	Delayed Alemtuzumab Treatment (DAT)	Initial Alemtuzumab Treatment (IAT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	241	598		
Units: score on a scale				
arithmetic mean (standard deviation)				
Month 12 (n=231,571)	-0.01 (± 0.26)	-0.01 (± 0.26)		
Month 24 (n=225,550)	-0.02 (± 0.28)	-0.01 (± 0.26)		
Month 36 (n=218,530)	-0.04 (± 0.27)	-0.00 (± 0.26)		
Month 48 (n=207,469)	-0.03 (± 0.27)	-0.03 (± 0.27)		
Month 60 (n=83,184)	-0.03 (± 0.29)	-0.03 (± 0.25)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in EQ-5D Visual Analogue Scale (VAS) Scores at Month 12, 24, 36, 48 and 60

End point title	Change From Baseline in EQ-5D Visual Analogue Scale (VAS) Scores at Month 12, 24, 36, 48 and 60

End point description:

EQ-5D VAS was used to record a subject's rating for his/her current health-related quality of life state and captured on a vertical VAS (0 to 100), where 0=worst imaginable health state to 100=best imaginable health state, and higher score indicated better outcome. Analysis was performed on efficacy population. Here, 'n' = subjects with available data for each specified category. As pre-specified, data collection and analysis for this endpoint was done only on the 2 subgroups (DAT and IAT).

End point type	Secondary

End point timeframe:

Baseline (Month 0 of LPS13649), Month 12, Month 24, Month 36, Month 48 and Month 60

End point values	Delayed Alemtuzumab Treatment (DAT)	Initial Alemtuzumab Treatment (IAT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	241	598		
Units: score on a scale				
arithmetic mean (standard deviation)				
Month 12 (n=232,560)	-2.09 (± 25.11)	-1.05 (± 24.57)		
Month 24 (n=225,545)	-1.57 (± 26.69)	-0.39 (± 21.44)		
Month 36 (n=217,527)	0.10 (± 22.61)	1.42 (± 20.64)		
Month 48 (n=199,466)	-1.08 (± 23.66)	-0.85 (± 23.94)		
Month 60 (n=82,177)	-3.26 (± 27.04)	-0.77 (± 26.26)		

Statistical analyses

No statistical analyses for this end point

Secondary: Modified Healthcare Resource Utilisation Questionnaire (HRUQ): Number of Subjects Who Reported Change in Employment Situation, Availing of Sick Leaves, Admissions and Stays in Hospital, Rehabilitation Centers or Nursing Homes Due to Multiple Sclerosis

End point title	Modified Healthcare Resource Utilisation Questionnaire (HRUQ): Number of Subjects Who Reported Change in Employment Situation, Availing of Sick Leaves, Admissions and Stays in Hospital, Rehabilitation Centers or Nursing Homes Due to Multiple Sclerosis

End point description:

Subjects use of healthcare resources, non-medical resources, and informal care as well as their work capacity was assessed at scheduled study visits using a modified questionnaire(HRUQ) designed to evaluate economic impact of MS. Questionnaire addresses following areas: employment situation & changes in employment situation;sick leave,admissions & stays in hospital, rehabilitation centers (RC)/nursing homes(NH); typical MS-related investments and devices (eg., walking aids, wheelchairs); assistance by community or social services (e.g., home nurse, transportation), or help from family/friends. Each question requires binary answer (yes/no). Subjects who reported "Yes" as an answer to the specified questions were reported. Efficacy population. Here, 'number of subjects analysed' = subjects evaluable for endpoint and 'n' = subjects with available data. Data collection and analysis for this endpoint was done on overall population along with 2 planned subgroups(DAT and IAT). "M"="months"

End point type	Secondary

End point timeframe:

Baseline (Month 0 of LPS13649), Month 12, Month 24, Month 36, Month 48 and Month 60

End point values	Alemtuzumab	Delayed Alemtuzumab Treatment (DAT)	Initial Alemtuzumab Treatment (IAT)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	1020	231	573	
Units: subjects				
Employment situation change:M0(n=381,84,224)	12	3	7	
Employment situation change:M12(n=1014,230,573)	44	11	25	
Employment situation change:M24(n=960,220,537)	40	14	19	
Employment situation change:M36(n=929,217,518)	44	12	26	
Employment situation change:M48(n=850,200,467)	38	4	24	
Employment situation change:M60(n=367,81,182)	14	3	8	
Had sick leave:M0(n= n=265,57,157)	21	6	14	
Had sick leave:M12(n=642,127,373)	77	19	45	
Had sick leave:M24(n=645,148,360)	80	23	42	
Had sick leave:M36(n=584,145,324)	78	21	44	
Had sick leave:M48(n=565,134,307)	60	18	31	
Had sick leave:M60(n=266,56,127)	25	9	10	
Had hospital admission:M0(n= n=337,73,203)	32	4	23	
Had hospital admission:M12(n=1018,231,570)	109	28	59	
Had hospital admission:M24(n=974,223,544)	95	26	53	
Had hospital admission:M36(n=938,218,522)	106	27	58	
Had hospital admission:M48(n=859,202,471)	89	20	51	

Had hospital admission:M60(n=374,81,184)	28	12	11	
Had spent time in RC:M0(n= n=334,74,200)	8	0	6	
Had spent time in RC:M12(n=1020,230,573)	45	12	21	
Had spent time in RC :M24(n=968,223,540)	45	17	18	
Had spent time in RC:M36(n=946,217,532)	36	12	19	
Had spent time in RC:M48(n=864,203,474)	45	12	24	
Had spent time in RC:M60(n=374,81,184)	18	5	6	
Had spent time in NH:M0(n= n=332,73,198)	0	0	0	
Had spent time in NH:M12(n=1019,229,572)	8	0	5	
Had spent time in NH :M24(n=972,222,545)	7	3	4	
Had spent time in NH:M36(n=938,218,523)	8	3	3	
Had spent time in NH:M48(n=860,202,472)	11	4	4	
Had spent time in NH:M60(n=369,81,184)	6	0	4	

Statistical analyses

No statistical analyses for this end point

Secondary: Modified HRUQ: Number of Subjects Who Reported Other Changes/Changes in Lifestyle Due to Multiple Sclerosis

End point title	Modified HRUQ: Number of Subjects Who Reported Other Changes/Changes in Lifestyle Due to Multiple Sclerosis

End point description:

Subjects use of healthcare resources, non-medical resources, and informal care as well as their work capacity was assessed at scheduled study visits using a modified questionnaire (HRUQ) designed to evaluate economic impact of MS. Questionnaire addresses following areas: employment situation and changes in employment situation;admissions & stays in hospital, rehabilitation centers/nursing homes; typical MS-related investments and devices (eg,walking aids, wheelchairs); assistance by community or social services (e.g.,home nurse, transportation), or help from family/friends. Each question requires a binary answer (yes/no). Subjects who reported "Yes" as an answer to the specified questions were reported. Efficacy population. ‘Number of subjects analysed’ = subjects evaluable for endpoint and 'n' = subjects with available data. Data collection and analysis for this endpoint was done on overall population along with 2 planned subgroups (DAT and IAT). "M" denotes "Month".

End point type	Secondary

End point timeframe:

Baseline (Month 0 of LPS13649), Month 12, Month 24, Month 36, Month 48 and Month 60

End point values	Alemtuzumab	Delayed Alemtuzumab Treatment (DAT)	Initial Alemtuzumab Treatment (IAT)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	1020	231	573	
Units: subjects				
Change to house, apartment,car:M 0(n=339,75,202)	7	0	3	
Change to house, apartment,car:M12(n=1020,231,571)	42	11	21	
Change to house,apartment,car:M 24(n=972,222,544)	47	10	25	
Change to house,apartment,car:M 36(n=944,219,527)	45	16	15	
Change to house,apartment,car:M 48(n=859,203,472)	42	10	25	
Change to house,apartment,car:M 60(n=372,80,185)	12	5	3	
Had required assistance:M 0(n=335,72,201)	24	4	10	
Had required assistance:M 12(n=1015,227,573)	88	24	45	
Had required assistance:M 24(n=962,221,535)	86	26	44	
Had required assistance:M 36(n=937,217,522)	79	22	35	
Had required assistance:M 48(n=852,203,466)	75	12	45	
Had required assistance:M 60(n=369,82,180)	26	8	10	
Had required other assistance:M 0(n=335,71,202)	77	15	48	
Had required other assistance:M 12(n=1011,226,572)	252	57	144	
Had required other assistance:M 24(n=958,222,530)	241	57	135	
Had required other assistance:M 36(n=936,217,523)	215	48	119	
Had required other assistance:M 48(n=848,201,463)	211	49	119	
Had required other assistance:M 60(n=367,82,180)	66	22	27	

Statistical analyses

No statistical analyses for this end point

Secondary: Health Related Productivity Questionnaire (HRPQ): Number of Subjects Reporting Current Employment Status (Part Time/Full Time/Not Employed) Due to Multiple Sclerosis

End point title	Health Related Productivity Questionnaire (HRPQ): Number of Subjects Reporting Current Employment Status (Part Time/Full Time/Not Employed) Due to Multiple Sclerosis

End point description:

Subjects use of healthcare resources, non-medical resources, and informal care as well as their work capacity was assessed at scheduled study visits using a modified questionnaire (HRPQ) designed to evaluate the economic impact of MS. The questionnaire addresses the following content area: subject

reported data regarding employment status, work productivity, impact on household chores due to MS. Current employment status of subjects (i.e. Part Time/Full Time/Not Employed) was reported in this endpoint. Analysis was performed on efficacy population. Here, 'number of subjects analysed' = subjects evaluable for this endpoint and 'n' = subjects with available data for each specified category. As pre-specified, data collection and analysis for this endpoint was done on the overall population along with the 2 subgroups (DAT and IAT).

End point type	Secondary

End point timeframe:

Baseline (Month 0 of LPS13649), Month 12, Month 24, Month 36, Month 48 and Month 60

End point values	Alemtuzumab	Delayed Alemtuzumab Treatment (DAT)	Initial Alemtuzumab Treatment (IAT)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	1025	234	575	
Units: subjects				
Full time: Month 0 (n=1025,234,575)	528	127	297	
Part time: Month 0 (n=1025,234,575)	98	20	54	
Not employed: Month 0 (n=1025,234,575)	399	87	224	
Full time: Month 12 (n=1013,229,569)	511	121	291	
Part time: Month 12 (n=1013,229,569)	104	20	53	
Not employed: Month 12 (n=1013,229,569)	398	88	225	
Full time: Month 24 (n=980,223,549)	488	118	273	
Part time: Month 24 (n=980,223,549)	117	21	66	
Not employed: Month 24 (n=980,223,549)	375	84	210	
Full time: Month 36 (n=943,216,530)	478	109	273	
Part time: Month 36 (n=943,216,530)	108	23	57	
Not employed: Month 36 (n=943,216,530)	357	84	200	
Full time: Month 48 (n=860,204,469)	424	108	225	
Part time: Month 48 (n=860,204,469)	103	21	57	
Not employed: Month 48 (n=860,204,469)	333	75	187	
Full time: Month 60 (n=374,82,183)	189	37	97	
Part time: Month 60 (n=374,82,183)	43	10	18	
Not employed: Month 60 (n=374,82,183)	142	35	68	

Statistical analyses

No statistical analyses for this end point

Secondary: HRPQ: Total Scheduled Working Hours and Number of Hours Missed From Work Due to Multiple Sclerosis

End point title	HRPQ: Total Scheduled Working Hours and Number of Hours Missed From Work Due to Multiple Sclerosis

End point description:

Subjects use of healthcare resources, non-medical resources, and informal care as well as their work capacity was assessed at scheduled study visits using a modified questionnaire (HRPQ) designed to evaluate the economic impact of MS. The questionnaire addresses the following content area: subject reported data regarding employment status, work productivity, impact on household chores due to MS. Data for "total scheduled working hours of subjects; number of hours missed from work by subjects due to MS" were reported in this endpoint. Analysis was performed on efficacy population. Here, 'number of subjects analysed' = subjects evaluable for this endpoint and 'n' = subjects with available data for each specified category. As pre-specified, data collection and analysis for this endpoint was done on the overall population along with the 2 subgroups (DAT and IAT).

End point type	Secondary

End point timeframe:

Baseline (Month 0 of LPS13649), Month 12, Month 24, Month 36, Month 48 and Month 60

End point values	Alemtuzumab	Delayed Alemtuzumab Treatment (DAT)	Initial Alemtuzumab Treatment (IAT)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	675	153	380	
Units: hours				
arithmetic mean (standard deviation)				
Total scheduled working hour:Month0(n=660,153,374)	32.9 (± 16.1)	34.0 (± 14.6)	32.2 (± 16.1)	
Total scheduled workinghour:Month12(n=675,152,380)	32.5 (± 16.6)	33.6 (± 15.4)	32.3 (± 16.6)	
Total scheduled workinghour:Month24(n=647,149,367)	31.6 (± 16.1)	33.2 (± 15.5)	30.8 (± 16.1)	
Total scheduled workinghour:Month36(n=615,137,343)	33.3 (± 15.3)	33.6 (± 16.4)	33.1 (± 15.1)	
Total scheduled workinghour:Month48(n=559,137,302)	32.9 (± 17.0)	34.4 (± 19.7)	31.3 (± 16.3)	
Total scheduled workinghour:Month60(n=249,52,124)	31.1 (± 16.6)	27.3 (± 18.9)	31.1 (± 15.8)	
Number of hours missed from work:Month0(n=39,8,21)	11.7 (± 12.8)	9.8 (± 12.1)	15.2 (± 15.0)	
Number of hour missed fromwork:Month12(n=47,14,23)	9.0 (± 10.2)	6.7 (± 3.6)	10.1 (± 12.2)	
Number of hour missed fromwork:Month24(n=41,9,22)	10.4 (± 10.9)	6.7 (± 6.1)	10.6 (± 11.3)	
Number of hour missed fromwork:Month36(n=35,6,21)	18.7 (± 50.8)	9.3 (± 5.9)	24.7 (± 65.4)	
Number of hour missed fromwork:Month48(n=42,11,21)	28.0 (± 77.1)	21.5 (± 23.1)	37.7 (± 107.6)	
umber of hour missed fromwork:Month60(n=12,2,5)	13.9 (± 13.0)	14.5 (± 13.4)	13.4 (± 13.4)	

Statistical analyses

No statistical analyses for this end point

Secondary: HRPQ: Percentage Impact on Work Output Due to Multiple Sclerosis

End point title	HRPQ: Percentage Impact on Work Output Due to Multiple Sclerosis

End point description:

Subjects use of healthcare resources, non-medical resources, and informal care as well as their work capacity was assessed at scheduled study visits using a modified questionnaire (HRPQ) designed to evaluate the economic impact of MS. The questionnaire addresses the following content area: subject reported data regarding employment status, work productivity, impact on household chores due to MS. Percentage impact on work output due to MS were reported in this endpoint. Analysis was performed on efficacy population. Here, 'number of subjects analysed' = subjects evaluable for this endpoint and 'n' = subjects with available data for each specified category. As pre-specified, data collection and analysis for this endpoint was done on the overall population along with the 2 subgroups (DAT and IAT).

End point type	Secondary

End point timeframe:

Baseline (Month 0 of LPS13649), Month 12, Month 24, Month 36, Month 48 and Month 60

End point values	Alemtuzumab	Delayed Alemtuzumab Treatment (DAT)	Initial Alemtuzumab Treatment (IAT)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	622	145	351	
Units: percentage impact on work output				
arithmetic mean (standard deviation)				
Month 0 (n=622,145,349)	8.5 (± 19.5)	6.2 (± 14.4)	10.2 (± 22.3)	
Month 12 (n=622,138,351)	9.0 (± 20.2)	8.7 (± 18.0)	9.5 (± 21.5)	
Month 24 (n=596,137,335)	9.8 (± 21.3)	9.9 (± 20.4)	9.4 (± 21.2)	
Month 36 (n=571,128,316)	9.4 (± 19.9)	9.2 (± 20.0)	9.9 (± 21.3)	
Month 48 (n=525,129,279)	9.7 (± 22.0)	12.2 (± 25.4)	9.3 (± 21.7)	
Month 60 (n=231,43,115)	9.2 (± 19.9)	11.7 (± 22.3)	8.1 (± 18.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: HRPQ: Total Scheduled Household Chores Hours; Number of Hours Missed From Household Chores Due to Multiple Sclerosis

End point title	HRPQ: Total Scheduled Household Chores Hours; Number of Hours Missed From Household Chores Due to Multiple Sclerosis

End point description:

Subjects use of healthcare resources, non-medical resources, and informal care as well as their work capacity was assessed at scheduled study visits using a modified questionnaire (HRPQ) designed to evaluate the economic impact of MS. Questionnaire addresses the following content area: subject reported data regarding employment status, work productivity, impact on household chores (HC) due to MS. Data for "total scheduled household chores hours; number of hours missed from planned household chores by subjects due to MS" were reported in this endpoint. Analysis was performed on efficacy population. Here, ` number of subjects analysed'=subjects evaluable for this endpoint and 'n'=subjects with available data for each specified category. As pre-specified, data collection and analysis for this endpoint was done on the overall population along with the 2 subgroups (DAT and IAT).

End point type	Secondary

End point timeframe:

Baseline (Month 0 of LPS13649), Month 12, Month 24, Month 36, Month 48 and Month 60

End point values	Alemtuzumab	Delayed Alemtuzumab Treatment (DAT)	Initial Alemtuzumab Treatment (IAT)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	1004	228	562	
Units: hours				
arithmetic mean (standard deviation)				
Total scheduled HC hours:Month 0(n=993,228,558)	10.8 (± 10.6)	9.8 (± 8.3)	11.0 (± 11.0)	
Total scheduled HC hours:Month 12(n=1004,226,562)	10.9 (± 11.5)	10.3 (± 10.1)	11.1 (± 11.7)	
Total scheduled HC hours:Month 24(n=954,219,538)	10.6 (± 11.4)	10.2 (± 11.6)	10.9 (± 11.4)	
Total scheduled HC hours:Month 36(n=899,203,505)	11.0 (± 12.1)	9.7 (± 10.2)	11.7 (± 13.1)	
Total scheduled HC hours:Month 48(n=825,193,452)	10.3 (± 10.3)	9.9 (± 8.9)	10.5 (± 10.6)	
Total scheduled HC hours:Month 60(n=363,77,178)	11.5 (± 12.6)	10.4 (± 8.7)	11.2 (± 11.1)	
Number of hour missed from HC:Month0(n=188,39,104)	6.0 (± 5.9)	4.7 (± 3.3)	6.5 (± 6.9)	
Number of hour missed from HC:Month12(n=173,47,90)	6.2 (± 6.6)	4.9 (± 3.5)	6.8 (± 7.7)	
Number of hour missed fromHC:Month24(n=181,35,104)	6.6 (± 9.3)	7.8 (± 9.0)	7.1 (± 10.6)	
Number of hour missed from HC:Month36(n=161,33,91)	7.0 (± 11.7)	6.1 (± 7.4)	7.7 (± 14.2)	
Number of hour missed from HC:Month48(n=143,37,74)	5.7 (± 8.4)	4.8 (± 4.3)	6.2 (± 10.6)	
Number of hour missed from HC:Month60(n=51,15,24)	5.9 (± 5.1)	5.3 (± 5.2)	5.8 (± 5.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: HRPQ: Percentage Impact on Work Output for Household Chores Due to Multiple Sclerosis

End point title	HRPQ: Percentage Impact on Work Output for Household Chores Due to Multiple Sclerosis

End point description:

Subjects use of healthcare resources, non-medical resources, and informal care as well as their work capacity was assessed at scheduled study visits using a modified questionnaire (HRPQ) designed to evaluate the economic impact of MS. The questionnaire addresses the following content area: subject reported data regarding employment status, work productivity, impact on household chores due to MS. Percentage impact on work output for household chores due to MS were reported in this endpoint. Analysis was performed on efficacy population. Here, 'number of subjects analysed' = subjects evaluable for this endpoint and 'n' = subjects with available data for each specified category. As pre-specified, data collection and analysis for this endpoint was planned to be done on the overall population along with the 2 planned subgroups (DAT and IAT).

End point type	Secondary

End point timeframe:

Baseline (Month 0 of LPS13649), Month 12, Month 24, Month 36, Month 48 and Month 60

End point values	Alemtuzumab	Delayed Alemtuzumab Treatment (DAT)	Initial Alemtuzumab Treatment (IAT)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	947	212	531	
Units: percentage impact on work output				
arithmetic mean (standard deviation)				
Month 0 (n=947,212,531)	16.8 (± 25.8)	16.0 (± 23.8)	16.4 (± 26.0)	
Month 12 (n=931,208,524)	17.7 (± 27.5)	18.3 (± 27.3)	16.6 (± 26.6)	
Month 24 (n=886,197,501)	19.4 (± 28.1)	20.3 (± 28.5)	18.5 (± 27.4)	
Month 36 (n=813,183,453)	17.6 (± 26.6)	17.5 (± 25.9)	16.5 (± 26.2)	
Month 48 (n=769,180,415)	18.6 (± 27.7)	19.8 (± 28.8)	17.0 (± 26.8)	
Month 60 (n=344,75,170)	14.8 (± 25.0)	18.8 (± 28.3)	13.1 (± 22.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: HRPQ: Duration of Disease (in Months) Since Development of Multiple Sclerosis

End point title	HRPQ: Duration of Disease (in Months) Since Development of Multiple Sclerosis

End point description:

Subjects use of healthcare resources, non-medical resources, and informal care as well as their work capacity was assessed at scheduled study visits using a modified questionnaire (HRPQ) designed to evaluate the economic impact of MS. The questionnaire addresses the following content area: subject reported data regarding employment status, work productivity, impact on household chores due to MS. Mean and standard deviation data for duration of MS disease (in months) since the start of MS development in subjects was reported in this endpoint. Analysis was performed on efficacy population. Here, 'number of subjects analysed' = subjects evaluable for this endpoint. As pre-specified, data collection and analysis for this endpoint was done on the overall population along with the 2 subgroups (DAT and IAT).

End point type	Secondary

End point timeframe:

Baseline up to end of the study (up to a maximum duration of 5.6 years)

End point values	Alemtuzumab	Delayed Alemtuzumab Treatment (DAT)	Initial Alemtuzumab Treatment (IAT)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	997	228	559	
Units: months				

arithmetic mean (standard deviation)	10.5 (± 4.5)	10.3 (± 4.0)	10.2 (± 5.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: HRPQ: Number of Subjects Who Reported Impact on Work Due to Multiple Sclerosis

End point title	HRPQ: Number of Subjects Who Reported Impact on Work Due to Multiple Sclerosis

End point description:

Subjects use of healthcare resources, non-medical resources, and informal care as well as their work capacity was assessed at scheduled study visits using a modified questionnaire (HRPQ) designed to evaluate the economic impact of MS. Questionnaire addresses following content area: subject reported data regarding employment status, work productivity, impact on household chores due to MS. Number of subjects who reported "Yes" an answer to "forced me to work part-time when I wanted to work full-time; kept me from having a job when I wanted to work full-time; kept me from having a job when I wanted to work part-time; none of the above" questions were reported in this endpoint. Analysis was performed on efficacy population. 'Number of subjects analysed' = subjects evaluable for this endpoint and 'n' = subjects with available data for each specified category. As pre-specified, data collection and analysis for this endpoint was done on overall population along with the 2 subgroups(DAT&IAT).

End point type	Secondary

End point timeframe:

Baseline up to end of the study (up to a maximum duration of 5.6 years)

End point values	Alemtuzumab	Delayed Alemtuzumab Treatment (DAT)	Initial Alemtuzumab Treatment (IAT)	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	709	164	399	
Units: subjects				
Work part-time,want to work full time(n=125,22,81)	125	22	81	
Kept from job,want to work full-time(n=168,32,88)	168	32	88	
Kept from job,want to work part-time(n=81,20,42)	81	20	42	
None of the above (n=709,164,399)	709	164	399	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs were collected from the Baseline until the end of the study (up to a maximum duration of 5.6 years).

Adverse event reporting additional description:

Reported AEs and death were TEAEs that is AEs that developed/worsened during the 'treatment period' (time from Baseline until the end of the study). Analysis was performed on safety population. As prespecified, safety analysis was done on the overall population along with 2 subgroups (DAT and IAT).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Delayed Alemtuzumab Treatment (DAT)

Reporting group description:

Subjects from the SC IFNB1a treatment arms of studies CAMMS323 and CAMMS324, who received their initial 2 treatment courses of alemtuzumab during the CAMMS03409 extension study were included in the DAT subgroup of the current study (LPS13649). Subjects received alemtuzumab intravenous infusion of 12 mg/day for 3 consecutive days, at the study investigators' discretion; and at least 12 months after the prior treatment course in the current study (LPS13649).

Reporting group title	Initial Alemtuzumab Treatment (IAT)

Reporting group description:

Subjects from the 12 mg/day alemtuzumab treatment arms of the studies CAMMS323 and CAMMS324 (who were subsequently enrolled in CAMMS03409 extension study and then entered in this study LPS13649) were included in the IAT subgroup of the current study (LPS13649). Subjects received alemtuzumab intravenous infusion of 12 mg/day for 3 consecutive days, at the study investigators' discretion; and at least 12 months after the prior treatment course in the current study (LPS13649).

Reporting group title	Alemtuzumab

Reporting group description:

All Subjects who completed the study CAMMS03409 (extension study of CAMMS223 [NCT00050778], CAMMS323 [NCT00530348], or CAMMS324 [NCT00548405]) and received alemtuzumab within 48 months prior to enrollment were included in this LPS13649 study. Subjects received alemtuzumab, intravenous infusion of 12 mg/day for 3 consecutive days, at the study investigators' discretion; and at least 12 months after the prior treatment course in the current study (LPS13649).

Serious adverse events	Delayed Alemtuzumab Treatment (DAT)	Initial Alemtuzumab Treatment (IAT)	Alemtuzumab
Total subjects affected by serious adverse events			
subjects affected / exposed	55 / 241 (22.82%)	133 / 598 (22.24%)	237 / 1062 (22.32%)
number of deaths (all causes)	0	10	11
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal Cell Carcinoma			

subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	2 / 1062 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 3	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast Cancer			
subjects affected / exposed	0 / 241 (0.00%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brenner Tumour			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervix Carcinoma Stage 0			
subjects affected / exposed	1 / 241 (0.41%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cutaneous T-Cell Lymphoma			
subjects affected / exposed	1 / 241 (0.41%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder Cancer Stage Iii			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intraductal Proliferative Breast Lesion			
subjects affected / exposed	1 / 241 (0.41%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive Ductal Breast Carcinoma			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	3 / 1062 (0.28%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive Lobular Breast Carcinoma			

subjects affected / exposed	1 / 241 (0.41%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal Squamous Cell Carcinoma			
subjects affected / exposed	1 / 241 (0.41%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung Squamous Cell Carcinoma Stage Iii			
subjects affected / exposed	0 / 241 (0.00%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant Melanoma			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant Melanoma In Situ			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant Neoplasm Of Unknown Primary Site			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
Neuroma			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-Hodgkin's Lymphoma			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian Adenoma			

subjects affected / exposed	1 / 241 (0.41%)	1 / 598 (0.17%)	2 / 1062 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian Cancer			
subjects affected / exposed	1 / 241 (0.41%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian Germ Cell Teratoma			
subjects affected / exposed	0 / 241 (0.00%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate Cancer			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal Cancer Metastatic			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
Squamous Cell Carcinoma Of Skin			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine Cancer			
subjects affected / exposed	1 / 241 (0.41%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine Leiomyoma			
subjects affected / exposed	1 / 241 (0.41%)	3 / 598 (0.50%)	5 / 1062 (0.47%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep Vein Thrombosis			

subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Flushing			
subjects affected / exposed	0 / 241 (0.00%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 241 (0.00%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral Artery Thrombosis			
subjects affected / exposed	0 / 241 (0.00%)	2 / 598 (0.33%)	2 / 1062 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion Missed			
subjects affected / exposed	0 / 241 (0.00%)	0 / 598 (0.00%)	2 / 1062 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abortion Spontaneous			
subjects affected / exposed	3 / 241 (1.24%)	6 / 598 (1.00%)	11 / 1062 (1.04%)
occurrences causally related to treatment / all	0 / 5	2 / 7	2 / 15
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anembryonic Gestation			
subjects affected / exposed	1 / 241 (0.41%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ectopic Pregnancy			
subjects affected / exposed	1 / 241 (0.41%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foetal Distress Syndrome			

subjects affected / exposed	0 / 241 (0.00%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hellp Syndrome			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Missed Labour			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pre-Eclampsia			
subjects affected / exposed	0 / 241 (0.00%)	2 / 598 (0.33%)	2 / 1062 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy			
subjects affected / exposed	2 / 241 (0.83%)	4 / 598 (0.67%)	7 / 1062 (0.66%)
occurrences causally related to treatment / all	0 / 3	0 / 4	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prolonged Labour			
subjects affected / exposed	0 / 241 (0.00%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Catheter Site Pain			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Complication Associated With Device			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			

subjects affected / exposed	0 / 241 (0.00%)	2 / 598 (0.33%)	2 / 1062 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 2
Drug Intolerance			
subjects affected / exposed	1 / 241 (0.41%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperthermia			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-Cardiac Chest Pain			
subjects affected / exposed	1 / 241 (0.41%)	1 / 598 (0.17%)	2 / 1062 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden Death			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Immune system disorders			
Drug Hypersensitivity			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune Reconstitution Inflammatory Syndrome			
subjects affected / exposed	1 / 241 (0.41%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	2 / 2	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sarcoidosis			

subjects affected / exposed	1 / 241 (0.41%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Cervical Dysplasia			
subjects affected / exposed	1 / 241 (0.41%)	3 / 598 (0.50%)	5 / 1062 (0.47%)
occurrences causally related to treatment / all	1 / 1	0 / 3	1 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystocele			
subjects affected / exposed	0 / 241 (0.00%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometriosis			
subjects affected / exposed	1 / 241 (0.41%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Female Genital Tract Fistula			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Menorrhagia			
subjects affected / exposed	1 / 241 (0.41%)	0 / 598 (0.00%)	2 / 1062 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metrorrhagia			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	2 / 1062 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine Polyp			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vaginal Haemorrhage			

subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute Respiratory Failure			
subjects affected / exposed	1 / 241 (0.41%)	1 / 598 (0.17%)	3 / 1062 (0.28%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			
subjects affected / exposed	1 / 241 (0.41%)	1 / 598 (0.17%)	2 / 1062 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atelectasis			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal Septum Deviation			
subjects affected / exposed	0 / 241 (0.00%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Organising Pneumonia			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Pneumomediastinum			
subjects affected / exposed	1 / 241 (0.41%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Embolism			

subjects affected / exposed	0 / 241 (0.00%)	3 / 598 (0.50%)	3 / 1062 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Fibrosis			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Alcoholism			
subjects affected / exposed	1 / 241 (0.41%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Behaviour Disorder			
subjects affected / exposed	1 / 241 (0.41%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Completed Suicide			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Confusional State			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	2 / 241 (0.83%)	2 / 598 (0.33%)	4 / 1062 (0.38%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression Suicidal			
subjects affected / exposed	1 / 241 (0.41%)	1 / 598 (0.17%)	2 / 1062 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug Abuse			

subjects affected / exposed	1 / 241 (0.41%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Major Depression			
subjects affected / exposed	0 / 241 (0.00%)	2 / 598 (0.33%)	2 / 1062 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental Disorder			
subjects affected / exposed	1 / 241 (0.41%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Substance-Induced Psychotic Disorder			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal Ideation			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide Attempt			
subjects affected / exposed	2 / 241 (0.83%)	2 / 598 (0.33%)	4 / 1062 (0.38%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Antiphospholipid Antibodies Positive			
subjects affected / exposed	1 / 241 (0.41%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Human Papilloma Virus Test Positive			
subjects affected / exposed	0 / 241 (0.00%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphocyte Count Decreased			

subjects affected / exposed	0 / 241 (0.00%)	2 / 598 (0.33%)	2 / 1062 (0.19%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Accidental Overdose			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle Fracture			
subjects affected / exposed	0 / 241 (0.00%)	2 / 598 (0.33%)	3 / 1062 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain Contusion			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Burns Third Degree			
subjects affected / exposed	0 / 241 (0.00%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Craniocerebral Injury			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Face Injury			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	1 / 241 (0.41%)	1 / 598 (0.17%)	2 / 1062 (0.19%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur Fracture			

subjects affected / exposed	1 / 241 (0.41%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot Fracture			
subjects affected / exposed	0 / 241 (0.00%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head Injury			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus Fracture			
subjects affected / exposed	1 / 241 (0.41%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Induced Abortion Failed			
subjects affected / exposed	0 / 241 (0.00%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intentional Overdose			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscus Injury			
subjects affected / exposed	0 / 241 (0.00%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post Procedural Hypotension			
subjects affected / exposed	1 / 241 (0.41%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius Fracture			

subjects affected / exposed	0 / 241 (0.00%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skull Fractured Base			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural Haematoma			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon Rupture			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia Fracture			
subjects affected / exposed	0 / 241 (0.00%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic Fracture			
subjects affected / exposed	0 / 241 (0.00%)	2 / 598 (0.33%)	2 / 1062 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulna Fracture			
subjects affected / exposed	1 / 241 (0.41%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper Limb Fracture			
subjects affected / exposed	0 / 241 (0.00%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist Fracture			

subjects affected / exposed	0 / 241 (0.00%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Atrial Septal Defect			
subjects affected / exposed	1 / 241 (0.41%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital Cystic Kidney Disease			
subjects affected / exposed	1 / 241 (0.41%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital Nail Disorder			
subjects affected / exposed	0 / 241 (0.00%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foetal Chromosome Abnormality			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Trisomy 21			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute Left Ventricular Failure			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute Myocardial Infarction			
subjects affected / exposed	1 / 241 (0.41%)	2 / 598 (0.33%)	4 / 1062 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Atrioventricular Block			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Bundle Branch Block Left			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary Artery Disease			
subjects affected / exposed	1 / 241 (0.41%)	0 / 598 (0.00%)	2 / 1062 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left Ventricular Dysfunction			
subjects affected / exposed	1 / 241 (0.41%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mitral Valve Incompetence			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial Infarction			
subjects affected / exposed	1 / 241 (0.41%)	1 / 598 (0.17%)	2 / 1062 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial Effusion			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus Tachycardia			
subjects affected / exposed	1 / 241 (0.41%)	0 / 598 (0.00%)	2 / 1062 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular Arrhythmia			

subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Ataxia			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysarthria			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	0 / 241 (0.00%)	2 / 598 (0.33%)	2 / 1062 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised Tonic-Clonic Seizure			
subjects affected / exposed	0 / 241 (0.00%)	2 / 598 (0.33%)	2 / 1062 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	2 / 241 (0.83%)	1 / 598 (0.17%)	3 / 1062 (0.28%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Limbic Encephalitis			

subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss Of Consciousness			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbosacral Radiculopathy			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple Sclerosis			
subjects affected / exposed	0 / 241 (0.00%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple Sclerosis Relapse			
subjects affected / exposed	6 / 241 (2.49%)	18 / 598 (3.01%)	30 / 1062 (2.82%)
occurrences causally related to treatment / all	0 / 6	0 / 30	0 / 43
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Optic Neuritis			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Partial Seizures			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post Herpetic Neuralgia			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postural Tremor			

subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Resting Tremor			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 241 (0.00%)	2 / 598 (0.33%)	2 / 1062 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxic Encephalopathy			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Trigeminal Neuralgia			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uhthoff's Phenomenon			
subjects affected / exposed	3 / 241 (1.24%)	5 / 598 (0.84%)	9 / 1062 (0.85%)
occurrences causally related to treatment / all	0 / 3	0 / 5	0 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile Neutropenia			

subjects affected / exposed	0 / 241 (0.00%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune Thrombocytopenia			
subjects affected / exposed	0 / 241 (0.00%)	2 / 598 (0.33%)	2 / 1062 (0.19%)
occurrences causally related to treatment / all	0 / 0	3 / 4	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphopenia			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	1 / 241 (0.41%)	2 / 598 (0.33%)	3 / 1062 (0.28%)
occurrences causally related to treatment / all	1 / 1	0 / 2	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Haematotympanum			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertigo			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine Ophthalmopathy			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Exophthalmos			

subjects affected / exposed	1 / 241 (0.41%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	2 / 2	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eyelid Ptosis			
subjects affected / exposed	1 / 241 (0.41%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glaucoma			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Optic Ischaemic Neuropathy			
subjects affected / exposed	0 / 241 (0.00%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periorbital Oedema			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal Pain Upper			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis Ulcerative			
subjects affected / exposed	0 / 241 (0.00%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 241 (0.41%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric Ulcer Perforation			

subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 241 (0.00%)	2 / 598 (0.33%)	3 / 1062 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	1 / 241 (0.41%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal Hernia			
subjects affected / exposed	0 / 241 (0.00%)	2 / 598 (0.33%)	2 / 1062 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal Ischaemia			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal Obstruction			
subjects affected / exposed	0 / 241 (0.00%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intussusception			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstructive Pancreatitis			

subjects affected / exposed	0 / 241 (0.00%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis Acute			
subjects affected / exposed	2 / 241 (0.83%)	0 / 598 (0.00%)	2 / 1062 (0.19%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis Chronic			
subjects affected / exposed	0 / 241 (0.00%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small Intestinal Obstruction			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	2 / 241 (0.83%)	0 / 598 (0.00%)	3 / 1062 (0.28%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	1 / 241 (0.41%)	2 / 598 (0.33%)	4 / 1062 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 241 (0.00%)	2 / 598 (0.33%)	2 / 1062 (0.19%)
occurrences causally related to treatment / all	0 / 0	1 / 3	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decubitus Ulcer			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erythema			

subjects affected / exposed	1 / 241 (0.41%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin Ulcer			
subjects affected / exposed	0 / 241 (0.00%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	1 / 241 (0.41%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis Haemorrhagic			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lupus Nephritis			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	2 / 241 (0.83%)	2 / 598 (0.33%)	5 / 1062 (0.47%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Colic			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Injury			

subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Autoimmune Hypothyroidism			
subjects affected / exposed	1 / 241 (0.41%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autoimmune Thyroid Disorder			
subjects affected / exposed	1 / 241 (0.41%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autoimmune Thyroiditis			
subjects affected / exposed	1 / 241 (0.41%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basedow's Disease			
subjects affected / exposed	2 / 241 (0.83%)	4 / 598 (0.67%)	7 / 1062 (0.66%)
occurrences causally related to treatment / all	2 / 2	4 / 4	7 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperthyroidism			
subjects affected / exposed	0 / 241 (0.00%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypothyroidism			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroid Dermatopathy			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back Pain			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint Contracture			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular Weakness			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal Pain			
subjects affected / exposed	0 / 241 (0.00%)	2 / 598 (0.33%)	2 / 1062 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis			
subjects affected / exposed	0 / 241 (0.00%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic Lupus Erythematosus			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal Abscess			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess Rupture			

subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal Abscess			
subjects affected / exposed	0 / 241 (0.00%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 241 (0.00%)	2 / 598 (0.33%)	2 / 1062 (0.19%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial Sepsis			
subjects affected / exposed	1 / 241 (0.41%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 241 (0.00%)	3 / 598 (0.50%)	4 / 1062 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 7	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis Staphylococcal			
subjects affected / exposed	0 / 241 (0.00%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium Difficile Colitis			
subjects affected / exposed	0 / 241 (0.00%)	2 / 598 (0.33%)	2 / 1062 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium Difficile Infection			

subjects affected / exposed	1 / 241 (0.41%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	1 / 241 (0.41%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis			
subjects affected / exposed	0 / 241 (0.00%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia Urinary Tract Infection			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gangrene			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal Bacterial Infection			
subjects affected / exposed	0 / 241 (0.00%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes Zoster			

subjects affected / exposed	0 / 241 (0.00%)	3 / 598 (0.50%)	3 / 1062 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes Zoster Infection Neurological			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected Bite			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected Lymphocele			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 241 (0.00%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Klebsiella Infection			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised Infection			
subjects affected / exposed	0 / 241 (0.00%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neonatal Pneumonia			
subjects affected / exposed	1 / 241 (0.41%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis Acute			

subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periodontitis			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 241 (0.41%)	4 / 598 (0.67%)	9 / 1062 (0.85%)
occurrences causally related to treatment / all	0 / 1	1 / 4	1 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia Bacterial			
subjects affected / exposed	0 / 241 (0.00%)	2 / 598 (0.33%)	2 / 1062 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia Streptococcal			
subjects affected / exposed	1 / 241 (0.41%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative Wound Infection			
subjects affected / exposed	0 / 241 (0.00%)	2 / 598 (0.33%)	2 / 1062 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	1 / 241 (0.41%)	1 / 598 (0.17%)	3 / 1062 (0.28%)
occurrences causally related to treatment / all	1 / 1	0 / 1	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Scrotal Abscess			
subjects affected / exposed	1 / 241 (0.41%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			

subjects affected / exposed	1 / 241 (0.41%)	2 / 598 (0.33%)	5 / 1062 (0.47%)
occurrences causally related to treatment / all	0 / 1	0 / 3	2 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic Shock			
subjects affected / exposed	0 / 241 (0.00%)	3 / 598 (0.50%)	4 / 1062 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 3
Urinary Tract Infection			
subjects affected / exposed	2 / 241 (0.83%)	4 / 598 (0.67%)	9 / 1062 (0.85%)
occurrences causally related to treatment / all	1 / 3	1 / 4	2 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary Tract Infection Bacterial			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	2 / 1062 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine Infection			
subjects affected / exposed	1 / 241 (0.41%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 241 (0.41%)	1 / 598 (0.17%)	2 / 1062 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes Mellitus			
subjects affected / exposed	0 / 241 (0.00%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic Ketosis			

subjects affected / exposed	0 / 241 (0.00%)	1 / 598 (0.17%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrolyte Imbalance			
subjects affected / exposed	1 / 241 (0.41%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	1 / 241 (0.41%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 1 Diabetes Mellitus			
subjects affected / exposed	0 / 241 (0.00%)	3 / 598 (0.50%)	3 / 1062 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 2 Diabetes Mellitus			
subjects affected / exposed	1 / 241 (0.41%)	0 / 598 (0.00%)	1 / 1062 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Delayed Alemtuzumab Treatment (DAT)	Initial Alemtuzumab Treatment (IAT)	Alemtuzumab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	150 / 241 (62.24%)	338 / 598 (56.52%)	601 / 1062 (56.59%)
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	15 / 241 (6.22%)	27 / 598 (4.52%)	54 / 1062 (5.08%)
occurrences (all)	20	34	74
Nervous system disorders			
Headache			
subjects affected / exposed	37 / 241 (15.35%)	67 / 598 (11.20%)	125 / 1062 (11.77%)
occurrences (all)	52	87	164

Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	14 / 241 (5.81%)	39 / 598 (6.52%)	63 / 1062 (5.93%)
occurrences (all)	23	46	86
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	15 / 241 (6.22%)	19 / 598 (3.18%)	43 / 1062 (4.05%)
occurrences (all)	17	19	45
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	13 / 241 (5.39%)	18 / 598 (3.01%)	37 / 1062 (3.48%)
occurrences (all)	13	18	37
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	13 / 241 (5.39%)	26 / 598 (4.35%)	51 / 1062 (4.80%)
occurrences (all)	16	34	64
Psychiatric disorders			
Depression			
subjects affected / exposed	13 / 241 (5.39%)	25 / 598 (4.18%)	43 / 1062 (4.05%)
occurrences (all)	13	26	45
Insomnia			
subjects affected / exposed	16 / 241 (6.64%)	29 / 598 (4.85%)	57 / 1062 (5.37%)
occurrences (all)	17	32	62
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	19 / 241 (7.88%)	39 / 598 (6.52%)	69 / 1062 (6.50%)
occurrences (all)	27	45	86
Back Pain			
subjects affected / exposed	16 / 241 (6.64%)	30 / 598 (5.02%)	62 / 1062 (5.84%)
occurrences (all)	16	34	68
Infections and infestations			
Bronchitis			
subjects affected / exposed	14 / 241 (5.81%)	44 / 598 (7.36%)	67 / 1062 (6.31%)
occurrences (all)	17	54	81
Herpes Zoster			

subjects affected / exposed	15 / 241 (6.22%)	29 / 598 (4.85%)	50 / 1062 (4.71%)
occurrences (all)	16	35	57
Influenza			
subjects affected / exposed	13 / 241 (5.39%)	25 / 598 (4.18%)	48 / 1062 (4.52%)
occurrences (all)	13	28	55
Nasopharyngitis			
subjects affected / exposed	34 / 241 (14.11%)	73 / 598 (12.21%)	129 / 1062 (12.15%)
occurrences (all)	60	112	204
Sinusitis			
subjects affected / exposed	11 / 241 (4.56%)	34 / 598 (5.69%)	57 / 1062 (5.37%)
occurrences (all)	11	45	71
Upper Respiratory Tract Infection			
subjects affected / exposed	27 / 241 (11.20%)	50 / 598 (8.36%)	96 / 1062 (9.04%)
occurrences (all)	29	73	123
Urinary Tract Infection			
subjects affected / exposed	37 / 241 (15.35%)	78 / 598 (13.04%)	151 / 1062 (14.22%)
occurrences (all)	56	143	271

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 February 2018	Following changes were made: To add an optional pharmacogenomics substudy for exploratory analysis of genetic variations predictive of autoimmune conditions; to harmonise the list of AESIs within sections; to clarify procedure for routine urinalysis and microscopy; to clarify timing of human papilloma virus screening in women; to clarify interim analysis objective; to update information regarding risk of Listeria infection according to new Lemtrada summary of product characteristics.
24 July 2019	Following changes were made: To provide information about new safety concerns that have been identified from post-marketing use with alemtuzumab. This includes reports of autoimmune hepatitis and hemophagocytic lymphohistiocytosis, as well as temporally associated serious cardiovascular reactions; to add measures to minimise the risks of subjects included in clinical trials.
28 January 2020	Following changes were made: To address safety update based on recent post marketing safety monitoring findings; to update contraindications for re-treatment with alemtuzumab; To update the list of AESIs within sections; to increase frequency of liver function tests from every 3 months to every month.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported