



Clinical trial results:

An Extension Protocol For Multiple Sclerosis Patients Who Participated in Genzyme-Sponsored Studies of Alemtuzumab

Summary

EudraCT number	2009-010788-18
Trial protocol	GB DE BE SE AT PL CZ NL DK ES IT
Global end of trial date	16 February 2016

Results information

Result version number	v1 (current)
This version publication date	05 March 2017
First version publication date	05 March 2017

Trial information

Trial identification

Sponsor protocol code	CAMMS03409
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00930553
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sanofi aventis recherche & développement
Sponsor organisation address	1 avenue Pierre Brossolette, Chilly-Mazarin, France, 91380
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	05 January 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	16 February 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objectives of the study were to examine:

- 1) the long term safety and efficacy of alemtuzumab in multiple sclerosis (MS) subjects who received alemtuzumab during prior company-sponsored studies CAMMS223, CAMMS323, and CAMMS324;
- 2) the safety and efficacy of as-needed alemtuzumab retreatment in these previously alemtuzumab-treated subjects;
- 3) the safety and efficacy of 2 fixed, annual, alemtuzumab courses followed by optional, as-needed, retreatment in subjects who had previously received subcutaneous (SC) interferon beta-1a (INFB-1a) during CAMMS223, CAMMS323, or CAMMS324.

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	05 August 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Poland: 59
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	Sweden: 7
Country: Number of subjects enrolled	United Kingdom: 100
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	Czech Republic: 27
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	Germany: 40

Country: Number of subjects enrolled	Italy: 14
Country: Number of subjects enrolled	Argentina: 7
Country: Number of subjects enrolled	Australia: 53
Country: Number of subjects enrolled	Brazil: 29
Country: Number of subjects enrolled	Canada: 33
Country: Number of subjects enrolled	Russian Federation: 158
Country: Number of subjects enrolled	Croatia: 133
Country: Number of subjects enrolled	Israel: 7
Country: Number of subjects enrolled	Mexico: 13
Country: Number of subjects enrolled	Serbia: 62
Country: Number of subjects enrolled	Ukraine: 67
Country: Number of subjects enrolled	United States: 471
Worldwide total number of subjects	1314
EEA total number of subjects	414

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)	1314
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This extension study enrolled subjects from previous 3 studies: CAMMS223 (NCT00050778), CAMMS323 (NCT00530348), and CAMMS324 (NCT00548405). Subjects were enrolled in this study only after their Month 24 visit in CAMMS323 and CAMMS324. CAMMS223 subjects were enrolled within 6 months once their site received approval of extension study.

Pre-assignment

Screening details:

Efficacy outcome data was analysed only on CAMMS323 and CAMMS324 subjects; safety data was analysed on all subjects, as pre-specified in protocol.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor ^[1]

Arms

Arm title	Alemtuzumab
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Arm description:

Subjects enrolled from any of the prior studies received long-term follow-up in this study. Subjects randomised to receive interferon beta-1a (IFNB-1a) in prior studies received alemtuzumab 12 mg/day infusion intravenously (IV) once daily (QD) for 5 consecutive days in treatment Course 1, and for 3 consecutive days in treatment Course 2, 12 months later in this study. Subjects who received 2 treatment courses with alemtuzumab could be treated with additional alemtuzumab courses of 12 mg/day infusion IV QD, for 3 consecutive days at least 48 weeks after the prior course if they had documented evidence of resumed disease activity (defined as ≥ 1 protocol-defined relapse and/or ≥ 2 new or enlarging brain or spinal lesions on magnetic resonance imaging [MRI]), unless they met safety-related retreatment disqualifying criteria.

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

Dosage and administration details:

Alemtuzumab was administered by IV infusion over a period of at least 4 hours.

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: Only outcome assessor was blinded in the study.

Number of subjects in period 1	Alemtuzumab
Started	1314
Completed	1091
Not completed	223
Other than specified above	28
Consent withdrawn by subject	88
Physician decision	39
Adverse events	1

Death	9
Pregnancy	1
Study terminated by sponsor	24
Lost to follow-up	25
Lack of efficacy	7
Protocol deviation	1

Baseline characteristics

Reporting groups

Reporting group title	Overall study
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Reporting group description:

Subjects enrolled from any of the previous studies received long-term follow-up in this study. Subjects randomised to receive IFNB-1a in any of the previous studies received alemtuzumab 12 mg/day infusion IV, QD for 5 consecutive days in treatment Course 1, and for 3 consecutive days in treatment Course 2, 12 months later in this study. Subjects who received 2 treatment courses with alemtuzumab could be treated with additional alemtuzumab courses of 12 mg/day infusion IV QD, for 3 consecutive days at least 48 weeks after the prior course if they had documented evidence of resumed disease activity (defined as ≥ 1 protocol-defined relapse and/or ≥ 2 new or enlarging brain or spinal lesions on MRI), unless they met safety-related retreatment disqualifying criteria.

Reporting group values	Overall study	Total	
Number of subjects	1314	1314	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	36.7 ± 8.51	-	
Gender categorical Units: Subjects			
Female	857	857	
Male	457	457	

End points

End points reporting groups

Reporting group title	Alemtuzumab
Reporting group description: Subjects enrolled from any of the prior studies received long-term follow-up in this study. Subjects randomised to receive interferon beta-1a (IFNB-1a) in prior studies received alemtuzumab 12 mg/day infusion intravenously (IV) once daily (QD) for 5 consecutive days in treatment Course 1, and for 3 consecutive days in treatment Course 2, 12 months later in this study. Subjects who received 2 treatment courses with alemtuzumab could be treated with additional alemtuzumab courses of 12 mg/day infusion IV QD, for 3 consecutive days at least 48 weeks after the prior course if they had documented evidence of resumed disease activity (defined as ≥ 1 protocol-defined relapse and/or ≥ 2 new or enlarging brain or spinal lesions on magnetic resonance imaging [MRI]), unless they met safety-related retreatment disqualifying criteria.	
Subject analysis set title	IFNB-1a/Alemtuzumab Switch CAMMS323/03409 (Pre Alemtuzumab)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects who received IFNB-1a in CAMMS323, were treated with alemtuzumab in CAMMS03409. IFNB-1a treatment period	
Subject analysis set title	IFNB-1a/Alemtuzumab Switch CAMMS323/03409 (Post Alemtuzumab)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects who received IFNB-1a in CAMMS323, were treated with alemtuzumab in CAMMS03409. Alemtuzumab treatment period	
Subject analysis set title	IFNB-1a/Alemtuzumab Switch CAMMS324/03409 (Pre Alemtuzumab)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects who received IFNB-1a in CAMMS324, were treated with alemtuzumab in CAMMS03409. IFNB-1a treatment period	
Subject analysis set title	IFNB-1a/Alemtuzumab Switch CAMMS324/03409 (Post Alemtuzumab)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects who received IFNB-1a in CAMMS324, were treated with alemtuzumab in CAMMS03409. Alemtuzumab treatment period	
Subject analysis set title	Alemtuzumab Retreatment
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects who received alemtuzumab in CAMMS323 (NCT00530348) or CAMMS324 (NCT00548405), received an additional course of alemtuzumab in this study.	
Subject analysis set title	Alemtuzumab Treatment CAMMS323 Extension
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects who were randomised to alemtuzumab 12 mg/day treatment in CAMMS323 (NCT00530348) and enrolled in enrolled in this extension study (CAMMS03409).	
Subject analysis set title	Alemtuzumab Treatment CAMMS324 Extension
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects who were randomised to alemtuzumab 12 mg/day treatment in CAMMS324 (NCT00548405) and enrolled in this extension study (CAMMS03409).	

Primary: Annualized Relapse Rate (ARR)

End point title	Annualized Relapse Rate (ARR) ^[1]
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End point description:

Relapse was defined as new neurological symptoms or worsening of previous neurological symptoms with an objective change on neurological examination, attributable to MS that last for at least 48 hours, present at normal body temperature, and that were preceded by at least 30 days of clinical stability. ARR was obtained from the total number of confirmed relapses that occurred during the treatment period divided by the sum of all subjects involved in certain treatment groups. ARR was estimated through negative binomial regression with robust variance estimation and covariate adjustment for geographic region. Subset of full analysis set (FAS - defined as all subjects randomised in CAMMS223, CAMMS323, and CAMMS324 and who received at least 1 dose of study drug)) included subjects who had received at least 1 dose of alemtuzumab in CAMMS323 and CAMMS324. Number of subjects analysed = Subjects with available data for this endpoint.

End point type	Primary
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End point timeframe:

Year 3, 4, 5, 6 from the Baseline (Month 0 of CAMMS323 and Month 0 of CAMMS324 for "Alemtuzumab Treatment CAMMS323 Extension" group and "Alemtuzumab Treatment CAMMS324 Extension" group, respectively)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive data was reported for this endpoint.

End point values	Alemtuzumab Treatment CAMMS323 Extension	Alemtuzumab Treatment CAMMS324 Extension		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	353	391		
Units: relapses per subject per year				
number (not applicable)				
Year 3	0.19	0.22		
Year 4	0.16	0.24		
Year 5	0.15	0.19		
Year 6	0.12	0.16		

Statistical analyses

No statistical analyses for this end point

Primary: Annualized Relapse Rate (ARR) Before and After Receiving Alemtuzumab

End point title	Annualized Relapse Rate (ARR) Before and After Receiving Alemtuzumab ^[2]
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End point description:

Relapse was defined as new neurological symptoms or worsening of previous neurological symptoms with an objective change on neurological examination, attributable to MS that last for at least 48 hours, present at normal body temperature, and that were preceded by at least 30 days of clinical stability. ARR was obtained from the total number of confirmed relapses that occurred during the treatment follow-up time of all subjects divided by the sum of total follow-up time of all subjects involved in certain treatment groups. ARR was estimated through repeated negative binomial regression with robust variance estimation and covariate adjustment for geographic region. The IFNB-1a/Alemtuzumab switch from CAMMS323 or CAMMS324 to CAMMS03409 pre alemtuzumab reporting group consisted of the same subjects as those in the corresponding post alemtuzumab reporting group. Subset of FAS who received IFNB-1a in CAMMS323 or CAMMS324 and who were treated with alemtuzumab in CAMMS03409.

End point type	Primary
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End point timeframe:

Baseline (Year 0 of initial studies) up to Year 4

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive data was reported for this endpoint.

End point values	IFNB-1a/Alemtuzumab Switch CAMMS323/03 409 (Pre Alemtuzumab)	IFNB-1a/Alemtuzumab Switch CAMMS323/03 409 (Post Alemtuzumab)	IFNB-1a/Alemtuzumab Switch CAMMS324/03 409 (Pre Alemtuzumab)	IFNB-1a/Alemtuzumab Switch CAMMS324/03 409 (Post Alemtuzumab)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	139	139	143	143
Units: relapses per subject per year				
number (confidence interval 95%)	0.42 (0.28 to 0.64)	0.14 (0.09 to 0.21)	0.6 (0.45 to 0.78)	0.15 (0.1 to 0.22)

Statistical analyses

No statistical analyses for this end point

Primary: Annualized Relapse Rate (ARR) Before and After Alemtuzumab Retreatment

End point title	Annualized Relapse Rate (ARR) Before and After Alemtuzumab Retreatment ^[3]
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End point description:

Relapse was defined as new neurological symptoms or worsening of previous neurological symptoms with an objective change on neurological examination, attributable to MS that last for at least 48 hours, present at normal body temperature, and that were preceded by at least 30 days of clinical stability. ARR was obtained from the total number of confirmed relapses that occurred during the treatment period divided by the sum of all subjects involved in certain treatment groups. ARR was estimated through negative binomial regression with robust variance estimation and covariate adjustment for geographic region. Subset of FAS included subjects who had received alemtuzumab in CAMMS323 or CAMMS324 and received an additional course of alemtuzumab in this extension study.

End point type	Primary
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End point timeframe:

Year 1 prior to retreatment, Year 1, 2, 3 after retreatment

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: Only descriptive data was reported for this endpoint.

End point values	Alemtuzumab Retreatment			
Subject group type	Subject analysis set			
Number of subjects analysed	321			
Units: relapses per subject per year				
number (confidence interval 95%)				
Year 1 prior to retreatment	0.79 (0.73 to 0.87)			
Year 1 after retreatment	0.18 (0.14 to 0.24)			

Year 2 after retreatment	0.29 (0.23 to 0.38)			
Year 3 after retreatment	0.3 (0.21 to 0.41)			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Sustained Accumulation of Disability (SAD)

End point title	Number of Subjects With Sustained Accumulation of Disability (SAD) ^[4]
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End point description:

SAD: increase of ≥ 1.5 points in Expanded Disability Status Scale (EDSS) score for subjects with prior study baseline score (PSBS) of 0 and increase of ≥ 1.0 point for subjects with a PSBS of 1.0 or more; persisted over a 6-month consecutive period. EDSS is ordinal scale in half-point increments, quantifying disability in subjects with MS. It assesses 7 functional systems (visual, brainstem, pyramidal, cerebellar, sensory, bowel/bladder, cerebral) and ambulation. EDSS total score ranges 0 (normal neurological examination) to 10 (death due to MS), higher scores indicating worse neurological function. Baseline was Year 0 of CAMMS323 and Year 0 of CAMMS324 for "alemtuzumab treatment CAMMS323 extension" and "alemtuzumab Treatment CAMMS324 Extension", respectively. Subset of full analysis set (FAS -all subjects randomised in CAMMS223, CAMMS323, and CAMMS324 and who received at least 1 dose of study drug) included subjects who had received at least 1 dose of alemtuzumab in CAMMS323 and CAMMS324.

End point type	Primary
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End point timeframe:

Baseline (Year 0) up to Year 6

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: Statistical analysis has been provided separately as an attachment.

End point values	Alemtuzumab Treatment CAMMS323 Extension	Alemtuzumab Treatment CAMMS324 Extension		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	376	426		
Units: subjects				
number (not applicable)	79	118		

Attachments (see zip file)	Statistical Analysis 1/Statistical Analysis Results 1.pdf
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Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Sustained Accumulation of Disability (SAD) Before and After Alemtuzumab Treatment: 2 Year Comparison

End point title	Number of Subjects With Sustained Accumulation of Disability (SAD) Before and After Alemtuzumab Treatment: 2 Year Comparison ^[5]
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End point description:

SAD: An increase of at least 1.5 points in EDSS score for subjects with PSBS of 0 and increase of at least 1.0 point for subjects with a PSBS of 1.0 or more; and the increase persisted over a 6-month consecutive period. EDSS is an ordinal scale in half-point increments that quantifies disability in subjects with MS. It assesses 7 functional systems (visual, brainstem, pyramidal, cerebellar, sensory, bowel/bladder and cerebral) and ambulation. EDSS total score ranges from 0 (normal neurological examination) to 10 (death due to MS), higher scores indicating worse neurological function. Number of subjects with SAD over 2 years before and 2 years after alemtuzumab treatment were estimated by Kaplan-Meier method. The IFNB-1a/Alemtuzumab switch pre alemtuzumab reporting group consisted of the same subjects as those in the corresponding post alemtuzumab reporting group. Subset of FAS who received IFNB-1a in CAMMS323 or CAMMS324 and who were treated with alemtuzumab in CAMMS03409.

End point type	Primary
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End point timeframe:

Baseline (Year 0 of initial studies) up to Year 4

Notes:

[5] - 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: Statistical analysis has been provided separately as an attachment.

End point values	IFNB-1a/Alemtuzumab Switch CAMMS323/03 409 (Pre Alemtuzumab)	IFNB-1a/Alemtuzumab Switch CAMMS323/03 409 (Post Alemtuzumab)	IFNB-1a/Alemtuzumab Switch CAMMS324/03 409 (Pre Alemtuzumab)	IFNB-1a/Alemtuzumab Switch CAMMS324/03 409 (Post Alemtuzumab)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	139	139	143	143
Units: subjects				
number (not applicable)	13	11	29	17

Attachments (see zip file)

Statistical Analysis 2/Statistical Analysis Results 2.pdf

Statistical analyses

No statistical analyses for this end point

**Secondary: Number of Subjects With Sustained Reduction in Disability (SRD)
Assessed by EDSS at Year 6**

End point title	Number of Subjects With Sustained Reduction in Disability (SRD) Assessed by EDSS at Year 6
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End point description:

SRD was defined as a ≥ 1 point decrease in EDSS score lasting ≥ 6 months. SRD is only applicable to subjects with a baseline EDSS score of ≥ 2.0 . EDSS is an ordinal scale in half-point increments that quantifies disability in subjects with MS. It assesses 7 functional systems (visual, brainstem, pyramidal, cerebellar, sensory, bowel/bladder and cerebral) as well as ambulation. EDSS total score ranges from 0 (normal neurological examination) to 10 (death due to MS), where higher scores indicate worse neurological function. Number of subjects with SRD at Year 6 was estimated using Kaplan-Meier method and reported in this endpoint. Subset of full analysis set (FAS - defined as all subjects randomised in CAMMS223, CAMMS323, and CAMMS324 and who received at least 1 dose of study drug) included subjectss who had received at least 1 dose of alemtuzumab in CAMMS323 and CAMMS324. Number of subjects analysed = subjects with available data for this endpoint.

End point type	Secondary
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End point timeframe:

Baseline (Year 0) up to Year 6

End point values	Alemtuzumab Treatment CAMMS323 Extension	Alemtuzumab Treatment CAMMS324 Extension		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	235	321		
Units: subjects				
number (not applicable)	74	130		

Attachments (see zip file)	Statistical Analysis 3/Statistical Analysis Results 3.pdf
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Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Sustained Reduction in Disability (SRD) Assessed by EDSS (After Alemtuzumab Treatment) at Year 2 of the Extension Study

End point title	Number of Subjects With Sustained Reduction in Disability (SRD) Assessed by EDSS (After Alemtuzumab Treatment) at Year 2 of the Extension Study
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End point description:

SRD: a ≥ 1 point decrease in EDSS score lasting ≥ 6 months. SRD is only applicable to subjects with baseline EDSS score of ≥ 2.0 . EDSS is an ordinal scale in half-point increments that quantifies disability in subjects with MS. It assesses 7 functional systems (visual, brainstem, pyramidal, cerebellar, sensory, bowel/bladder and cerebral) as well as ambulation. EDSS total score ranges from 0 (normal neurological examination) to 10 (death due to MS), where higher scores indicate worse neurological function. Number of subjects with SRD at Year 2 of CAMMS03409 was estimated using Kaplan-Meier method. The IFNB-1a/Alemtuzumab switch from CAMMS323 or CAMMS324 to CAMMS03409 pre alemtuzumab reporting group consisted of the same subjects as those in the corresponding post alemtuzumab reporting group. Subset of FAS who received IFNB-1a in CAMMS323 or CAMMS324 and who were treated with alemtuzumab in CAMMS03409. Number of subjects analysed = subjects with available data for this endpoint.

End point type	Secondary
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End point timeframe:

Extension study (CAMMS03409) baseline up to Extension Year 2

End point values	IFNB-1a/Alemtuzumab Switch CAMMS323/03409 (Post Alemtuzumab)	IFNB-1a/Alemtuzumab Switch CAMMS324/03409 (Post Alemtuzumab)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	65	102		
Units: subjects				
number (not applicable)	11	14		

Attachments (see zip file)	Statistical Analysis 4/Statistical Analysis Results 4.pdf
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Statistical analyses

No statistical analyses for this end point

Secondary: Change From Initial Study Baseline in EDSS Score at Year 3, 4, 5 and 6

End point title	Change From Initial Study Baseline in EDSS Score at Year 3, 4, 5 and 6
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End point description:

EDSS is an ordinal scale in half-point increments that quantifies disability in participants with MS. It assesses the 7 functional systems (visual, brainstem, pyramidal, cerebellar, sensory, bowel/bladder and cerebral) as well as ambulation. EDSS total score ranges from 0 (normal neurological examination) to 10 (death due to MS), where higher scores indicate worse neurological function. Change was calculated by subtracting baseline (Month 0 of the study CAMMS323 [NCT00530348] or CAMMS324 [NCT00548405]) value from EDSS scores at specified time points. Subset of full analysis set (FAS - defined as all subjects randomised in CAMMS223, CAMMS323, and CAMMS324 and who received at least 1 dose of study drug) included subjects who had received at least 1 dose of alemtuzumab in CAMMS323 and CAMMS324. Number of subjects analysed = subjects with available data for this endpoint.

End point type	Secondary
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End point timeframe:

Baseline (Month 0 of CAMMS323 and Month 0 of CAMMS324 for "Alemtuzumab Treatment CAMMS323 Extension" group and "Alemtuzumab Treatment CAMMS324 Extension" group, respectively), Year 3, 4, 5, 6

End point values	Alemtuzumab Treatment CAMMS323 Extension	Alemtuzumab Treatment CAMMS324 Extension		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	326	370		
Units: units on a scale				
arithmetic mean (confidence interval 95%)				
Change at Year 3	-0.08 (-0.2 to 0.04)	-0.02 (-0.14 to 0.1)		
Change at Year 4	-0.06 (-0.19 to 0.07)	0.06 (-0.07 to 0.19)		
Change at Year 5	0.06 (-0.08 to 0.19)	0.13 (-0.01 to 0.27)		
Change at Year 6	0.09 (-0.04 to 0.23)	0.18 (0.03 to 0.32)		

Statistical analyses

Secondary: Change From Initial Study Baseline in EDSS Score Before and After Alemtuzumab Treatment: 2 Year Comparison

End point title	Change From Initial Study Baseline in EDSS Score Before and After Alemtuzumab Treatment: 2 Year Comparison
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End point description:

EDSS is an ordinal scale in half-point increments that quantifies disability in subjects with MS. It assesses the 7 functional systems (visual, brainstem, pyramidal, cerebellar, sensory, bowel/bladder and cerebral) as well as ambulation. EDSS total score ranges from 0 (normal neurological examination) to 10 (death due to MS), where higher scores indicate worse neurological function. Change was calculated by subtracting baseline (Month 0 of the study CAMMS323 or CAMMS324 for pre alemtuzumab period or CAMMS03409 baseline for post alemtuzumab period) value, from EDSS scores at specified time points. The IFNB-1a/Alemtuzumab switch pre alemtuzumab reporting group consisted of the same subjects as those in the corresponding post alemtuzumab reporting groups. Baseline was Year 0 of CAMMS323 and Year 0 of CAMMS324 for "CAMMS323" and "CAMMS324" subjects, respectively. Subset of FAS who received IFNB-1a in CAMMS323 or CAMMS324 and who were treated with alemtuzumab in CAMMS03409.

End point type	Secondary
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End point timeframe:

Baseline (Year 0 of initial studies) up to Year 4

End point values	IFNB-1a/Alemtuzumab Switch CAMMS323/03409 (Pre Alemtuzumab)	IFNB-1a/Alemtuzumab Switch CAMMS323/03409 (Post Alemtuzumab)	IFNB-1a/Alemtuzumab Switch CAMMS324/03409 (Pre Alemtuzumab)	IFNB-1a/Alemtuzumab Switch CAMMS324/03409 (Post Alemtuzumab)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	139	139	143	143
Units: units on a scale				
arithmetic mean (confidence interval 95%)				
Year 0 -2	-0.15 (-0.32 to 0.03)	-0.07 (-0.23 to 0.09)	0.11 (-0.05 to 0.26)	-0.02 (-0.18 to 0.14)
Year 3 - 4	-0.21 (-0.43 to 0)	0.08 (-0.11 to 0.27)	0.2 (-0.01 to 0.41)	0.13 (-0.05 to 0.31)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Retreatment Baseline in EDSS Score After Alemtuzumab Retreatment

End point title	Change From Retreatment Baseline in EDSS Score After Alemtuzumab Retreatment
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End point description:

EDSS is an ordinal scale in half-point increments that quantifies disability in subjects with MS. It assesses the 7 functional systems (visual, brainstem, pyramidal, cerebellar, sensory, bowel/bladder and cerebral) as well as ambulation. EDSS total score ranges from 0 (normal neurological examination) to 10 (death due to MS), where higher scores indicate worse neurological function. Change was calculated by subtracting retreatment baseline (annual visit prior to the retreatment start date) value from EDSS scores at specified time points. Subset of FAS included subjects who had received alemtuzumab in CAMMS323 or CAMMS324 and received an additional course of alemtuzumab in this extension study.

End point type	Secondary
End point timeframe:	
Retreatment baseline, Year 1, 2 and 3 after retreatment baseline	

End point values	Alemtuzumab Retreatment			
Subject group type	Subject analysis set			
Number of subjects analysed	321			
Units: units on a scale				
arithmetic mean (standard deviation)				
Retreatment baseline (n = 307)	2.89 (± 1.514)			
Change at Year 1 after retreatment baseline(n=256)	-0.22 (± 1.033)			
Change at Year 2 after retreatment baseline(n=158)	-0.13 (± 1.109)			
Change at Year 3 after retreatment baseline(n=75)	0.07 (± 1.356)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Without New or Enlarging Magnetic Resonance Imaging (MRI)-T2-Hypertense Lesion Activity

End point title	Percentage of Subjects Without New or Enlarging Magnetic Resonance Imaging (MRI)-T2-Hypertense Lesion Activity
End point description:	
Analysis of new or enlarging lesions that appear hyperintense on T2-weighted MRI scans performed annually. Subset of full analysis set (FAS - defined as all subjects randomised in CAMMS223, CAMMS323, and CAMMS324 and who received at least 1 dose of study drug) included subjects who had received at least 1 dose of alemtuzumab in CAMMS323 and CAMMS324. Number of subjects analysed = subjects with available data for this endpoint.	
End point type	Secondary
End point timeframe:	
Year 3, 4, 5 and 6	

End point values	Alemtuzumab Treatment CAMMS323 Extension	Alemtuzumab Treatment CAMMS324 Extension		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	328	356		
Units: percentage of subjects				
number (not applicable)				
Year 3 (n = 328, 356)	72.6	68.8		
Year 4 (n = 323, 332)	70.3	70.2		
Year 5 (n = 319, 321)	70.2	67		

Year 6 (n = 307, 312)	66.8	69.6		
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Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Without New or Enlarging MRI-T2-Hypertense Lesion Activity Before and After Alemtuzumab Treatment

End point title	Percentage of Subjects Without New or Enlarging MRI-T2-Hypertense Lesion Activity Before and After Alemtuzumab Treatment
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End point description:

Analysis of new or enlarging lesions that appear hyperintense on T2-weighted MRI scans performed annually. The IFNB-1a/Alemtuzumab switch from CAMMS323 or CAMMS324 to CAMMS03409 pre alemtuzumab reporting group consisted of the same subjects as those in the corresponding post alemtuzumab reporting group. Subset of FAS who received IFNB-1a in CAMMS323 or CAMMS324 and who were treated with alemtuzumab in CAMMS03409. Here 'n' signifies number of subjects with available data for specified category.

End point type	Secondary
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End point timeframe:

Baseline (Year 0 of initial studies) up to Year 4

End point values	IFNB-1a/Alemtuzumab Switch CAMMS323/03409 (Pre Alemtuzumab)	IFNB-1a/Alemtuzumab Switch CAMMS323/03409 (Post Alemtuzumab)	IFNB-1a/Alemtuzumab Switch CAMMS324/03409 (Pre Alemtuzumab)	IFNB-1a/Alemtuzumab Switch CAMMS324/03409 (Post Alemtuzumab)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	139	139	143	143
Units: percentage of subjects				
number (not applicable)				
Year 0 - 1 (n = 135, 135, 139, 138)	57	79.3	44.6	63.8
Year 0 - 2 (n = 135, 132, 139, 131)	60.7	81.8	47.5	81.7

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Without New or Enlarging MRI-T2-Hypertense Lesion Activity Before and After Alemtuzumab Retreatment

End point title	Percentage of Subjects Without New or Enlarging MRI-T2-Hypertense Lesion Activity Before and After Alemtuzumab Retreatment
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End point description:

Analysis of new or enlarging lesions that appear hyperintense on T2-weighted MRI scans performed

annually. Retreatment baseline was the annual visit prior to the retreatment start date. Subset of FAS included subjects who had received alemtuzumab in CAMMS323 or CAMMS324 and received an additional course of alemtuzumab in this extension study. Here 'n' signifies number of subjects with available data for specified category.

End point type	Secondary
End point timeframe:	
Retreatment Baseline, Year 1, 2 and 3 after retreatment	

End point values	Alemtuzumab Retreatment			
Subject group type	Subject analysis set			
Number of subjects analysed	321			
Units: percentage of subjects				
number (not applicable)				
Retreatment baseline (n = 315)	49.2			
Year 1 after retreatment baseline (n = 301)	64.1			
Year 2 after retreatment baseline (n = 197)	66			
Year 3 after retreatment baseline (n = 113)	60.2			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change From Baseline in MRI-T2-Hypertense Lesion Volumes at Year 3, 4, 5, 6

End point title	Percentage Change From Baseline in MRI-T2-Hypertense Lesion Volumes at Year 3, 4, 5, 6
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End point description:

Lesion volume was quantitatively assessed by hyperintensity on T2-weighted MRI scans. Subset of full analysis set (FAS - defined as all subjects randomised in CAMMS223, CAMMS323, and CAMMS324 and who received at least 1 dose of study drug) included subjects who had received at least 1 dose of alemtuzumab in CAMMS323 and CAMMS324. Here 'n' signifies number of subjects with available data for specified category.

End point type	Secondary
End point timeframe:	
Baseline (Month 0 of CAMMS323 and Month 0 of CAMMS324 for "Alemtuzumab Treatment CAMMS323 Extension" group and "Alemtuzumab Treatment CAMMS324 Extension" group, respectively), Year 3, 4, 5, 6	

End point values	Alemtuzumab Treatment CAMMS323 Extension	Alemtuzumab Treatment CAMMS324 Extension		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	332	364		
Units: percent change				
arithmetic mean (standard deviation)				
Change at Year 3 (n = 332, 364)	-6.57 (± 29.96)	1.69 (± 31.62)		
Change at Year 4 (n = 327, 339)	-5.04 (± 32.88)	4.97 (± 41.11)		
Change at Year 5 (n = 324, 336)	-4.09 (± 36.99)	12.37 (± 80.74)		
Change at Year 6 (n = 309, 319)	-2.68 (± 42.92)	11.46 (± 73.91)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Without New Gadolinium-enhancing MRI Lesion Activity

End point title	Percentage of Subjects Without New Gadolinium-enhancing MRI Lesion Activity
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End point description:

Analysis of new gadolinium-enhancing lesions that appear on MRI scans performed annually. Baseline was the prior annual visit. Subset of full analysis set (FAS - defined as all subjects randomised in CAMMS223, CAMMS323, and CAMMS324 and who received at least 1 dose of study drug) included subjects who had received at least 1 dose of alemtuzumab in CAMMS323 and CAMMS324. Number of subjects analysed = subjects with available data for this endpoint. Here 'n' signifies number of subjects with available data for specified category.

End point type	Secondary
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End point timeframe:

Year 3, 4, 5 and 6

End point values	Alemtuzumab Treatment CAMMS323 Extension	Alemtuzumab Treatment CAMMS324 Extension		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	330	356		
Units: percentage of subjects				
number (not applicable)				
Year 3 (n = 330, 356)	90.6	86.5		
Year 4 (n = 325, 331)	87.1	88.8		
Year 5 (n = 321, 321)	87.5	89.4		
Year 6 (n = 308, 310)	86.7	90		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Brain Parenchymal Fractions (BPF) at Year 3, 4, 5 and 6

End point title	Percent Change From Baseline in Brain Parenchymal Fractions (BPF) at Year 3, 4, 5 and 6
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End point description:

Brain parenchymal fraction (calculated as the ratio of brain parenchymal volume to total intradural volume), is a sensitive indicator of brain atrophy. Subset of full analysis set (FAS - defined as all subjects randomised in CAMMS223, CAMMS323, and CAMMS324 and who received at least 1 dose of study drug) included subjects who had received at least 1 dose of alemtuzumab in CAMMS323 and CAMMS324. Number of subjects analysed = subjects with available data for this endpoint. Here 'n' signifies number of subjects with available data for specified category.

End point type	Secondary
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End point timeframe:

Baseline (Month 0 of CAMMS323 and Month 0 of CAMMS324 for "Alemtuzumab Treatment CAMMS323 Extension" group and "Alemtuzumab Treatment CAMMS324 Extension" group, respectively), Year 3, 4, 5 and 6

End point values	Alemtuzumab Treatment CAMMS323 Extension	Alemtuzumab Treatment CAMMS324 Extension		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	325	355		
Units: percent change				
arithmetic mean (standard deviation)				
Change at Year 3 (n = 325, 355)	-1.068 (± 1.185)	-0.761 (± 1.24)		
Change at Year 4 (n = 323, 331)	-1.251 (± 1.228)	-0.949 (± 1.341)		
Change at Year 5 (n = 321, 317)	-1.437 (± 1.317)	-0.983 (± 1.374)		
Change at Year 6 (n = 308, 315)	-1.601 (± 1.37)	-1.051 (± 1.472)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Relapse Free Subjects

End point title	Percentage of Relapse Free Subjects
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End point description:

Relapse was defined as new neurological symptoms or worsening of previous neurological symptoms with an objective change on neurological examination, attributable to MS that last for at least 48 hours, present at normal body temperature, and that were preceded by at least 30 days of clinical stability. Subset of full analysis set (FAS - defined as all subjects randomised in CAMMS223, CAMMS323, and CAMMS324 and who received at least 1 dose of study drug) included subjects who had received at least 1 dose of alemtuzumab in CAMMS323 and CAMMS324. Number of subjects analysed = subjects with available data for this endpoint.

End point type	Secondary
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End point timeframe:

Year 3, 4, 5 and 6

End point values	Alemtuzumab Treatment CAMMS323 Extension	Alemtuzumab Treatment CAMMS324 Extension		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	353	391		
Units: percentage of subjects				
number (not applicable)				
Year 3	84.14	80.56		
Year 4	86.84	79.27		
Year 5	87.35	83.29		
Year 6	88.96	86.86		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Physical Component Score (PCS) of Short Form-36 (SF-36) Health Survey at Year 3, 4, 5 and 6

End point title	Change From Baseline in Physical Component Score (PCS) of Short Form-36 (SF-36) Health Survey at Year 3, 4, 5 and 6
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End point description:

SF-36 is a subject reported standardized survey designed to assess generic health related quality of life. It consisted of 36 items evaluating 8 aspects of functional health and well-being: 1) physical functioning, 2) role physical, 3) bodily pain, 4) general health, 5) vitality, 6) social functioning, 7) role emotional and 8) mental health. The score range for each of the 8 health aspects was from 0 (poor health) to 100 (better health), higher scores indicating good health condition. Scores of first four health aspects (1 - 4) were aggregated to derive the PCS ranging from 0 (worst) to 100 (best), where higher scores indicated good health condition. Subset of full analysis set (FAS - defined as all subjects randomised in CAMMS223, CAMMS323, and CAMMS324 and who received at least 1 dose of study drug) included subjects who had received at least 1 dose of alemtuzumab in CAMMS323 and CAMMS324. Number of subjects analysed = subjects with available data for this endpoint.

End point type	Secondary
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End point timeframe:

Baseline (Month 0 of CAMMS323 and Month 0 of CAMMS324 for "alemtuzumab treatment CAMMS323 extension group", "alemtuzumab Treatment CAMMS324 Extension" group, respectively), Year 3, 4, 5 and 6

End point values	Alemtuzumab Treatment CAMMS323 Extension	Alemtuzumab Treatment CAMMS324 Extension		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	340	375		
Units: units on a scale				
arithmetic mean (confidence interval)				

95%)				
Change at Year 3	1.9 (0.85 to 2.95)	1.72 (0.84 to 2.6)		
Change at Year 4	2.15 (1.1 to 3.2)	1.34 (0.4 to 2.28)		
Change at Year 5	1.85 (0.75 to 2.94)	1.34 (0.39 to 2.29)		
Change at Year 6	1.65 (0.56 to 2.74)	1 (-0.03 to 2.03)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Physical Component Score (PCS) of Short Form-36 (SF-36) Health Survey (Before and After Alemtuzumab Treatment): 2 Year Comparison

End point title	Change From Baseline in Physical Component Score (PCS) of Short Form-36 (SF-36) Health Survey (Before and After Alemtuzumab Treatment): 2 Year Comparison
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End point description:

SF-36 is a standardised survey designed to assess generic health related quality of life. It consisted of 36 items evaluating 8 aspects of functional health and well-being: 1) physical functioning, 2) role physical, 3) bodily pain, 4) general health, 5) vitality, 6) social functioning, 7) role emotional and 8) mental health. The score range for each health aspects was from 0 (poor health) to 100 (better health), higher scores indicating good health. Scores of first four health aspects (1 - 4) were aggregated to derive the PCS ranging from 0 (worst) to 100 (best), higher scores indicating good health. The IFNB-1a/Alemtuzumab switch from CAMMS323 or CAMMS324 to CAMMS03409 pre alemtuzumab group consisted of same subjects as those in corresponding post alemtuzumab group. Baseline was Year 0 of CAMMS323 and Year 0 of CAMMS324 for "CAMMS323" and "CAMMS324" subjects, respectively. Subset of FAS who received IFNB-1a in CAMMS323 or CAMMS324 and who were treated with alemtuzumab in CAMMS03409.

End point type	Secondary
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End point timeframe:

Baseline (Year 0 of initial studies) up to Year 4

End point values	IFNB-1a/Alemtuzumab Switch CAMMS323/03409 (Pre Alemtuzumab)	IFNB-1a/Alemtuzumab Switch CAMMS323/03409 (Post Alemtuzumab)	IFNB-1a/Alemtuzumab Switch CAMMS324/03409 (Pre Alemtuzumab)	IFNB-1a/Alemtuzumab Switch CAMMS324/03409 (Post Alemtuzumab)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	139	139	143	143
Units: units on a scale				
arithmetic mean (confidence interval 95%)				
Year 1	1.16 (-0.48 to 2.81)	2 (0.43 to 3.57)	0.79 (-0.34 to 1.93)	1.56 (0.38 to 2.75)
Year 2	1.2 (-0.54 to 2.95)	0.41 (-1.21 to 2.04)	0.45 (-0.86 to 1.76)	1.31 (0.14 to 2.48)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Mental Component Score (MCS) of Short Form-36 (SF-36) at Year 3, 4, 5, and 6

End point title	Change From Baseline in Mental Component Score (MCS) of Short Form-36 (SF-36) at Year 3, 4, 5, and 6
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End point description:

SF-36 is a subject reported standardized survey designed to assess generic health related quality of life. It consisted of 36 items evaluating 8 aspects of functional health and well-being: 1) physical functioning, 2) role physical, 3) bodily pain, 4) general health, 5) vitality, 6) social functioning, 7) role emotional and 8) mental health. The score range for each of the 8 health aspects was from 0 (poor health) to 100 (better health), higher scores indicating good health condition. Scores of last four health aspects (5 - 8) were aggregated to derive the MCS ranging from 0 (worst) to 100 (best), where higher scores indicated good health condition. Subset of full analysis set (FAS - defined as all subjects randomised in CAMMS223, CAMMS323, and CAMMS324 and who received at least 1 dose of study drug) included subjects who had received at least 1 dose of alemtuzumab in CAMMS323 and CAMMS324. Number of subjects analysed = subjects with available data for this endpoint.

End point type	Secondary
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End point timeframe:

Baseline (Month 0 of CAMMS323 and Month 0 of CAMMS324 for "Alemtuzumab Treatment CAMMS323 Extension" group and "Alemtuzumab Treatment CAMMS324 Extension" group, respectively), Year 3, 4, 5 and 6

End point values	Alemtuzumab Treatment CAMMS323 Extension	Alemtuzumab Treatment CAMMS324 Extension		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	340	375		
Units: units on a scale				
arithmetic mean (confidence interval 95%)				
Change at Year 3	2.43 (1.07 to 3.78)	1.96 (0.85 to 3.07)		
Change at Year 4	3.17 (1.85 to 4.49)	1.91 (0.77 to 3.05)		
Change at Year 5	2.54 (1.23 to 3.85)	1.75 (0.59 to 2.92)		
Change at Year 6	2.41 (1.01 to 3.8)	1.58 (0.35 to 2.82)		

Statistical analyses

Secondary: Change From Baseline in Mental Component Score (MCS) of Short Form-36 (SF-36) Before and After Alemtuzumab Treatment: 2 Year Comparison

End point title	Change From Baseline in Mental Component Score (MCS) of Short Form-36 (SF-36) Before and After Alemtuzumab Treatment: 2 Year Comparison
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End point description:

SF-36 is a standardized survey designed to assess generic health related quality of life. It consisted of 36 items evaluating 8 aspects of functional health and well-being: 1) physical functioning, 2) role physical, 3) bodily pain, 4) general health, 5) vitality, 6) social functioning, 7) role emotional and 8) mental health. The score range for each health aspects was from 0 (poor health) to 100 (better health), higher scores indicating good health. Scores of last four health aspects (5 - 8) were aggregated to derive the MCS ranging from 0 (worst) to 100 (best), higher scores indicating good health. The IFNB-1a/Alemtuzumab switch from CAMMS323 or CAMMS324 to CAMMS03409 pre alemtuzumab group consisted of same subjects as those in corresponding post alemtuzumab group. Baseline was Year 0 of CAMMS323 and Year 0 of CAMMS324 for "CAMMS323" and "CAMMS324" subjects, respectively. Subset of FAS who received IFNB-1a in CAMMS323 or CAMMS324 and who were treated with alemtuzumab in CAMMS03409.

End point type	Secondary
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End point timeframe:

Baseline (Year 0 of initial studies) up to Year 4

End point values	IFNB-1a/Alemtuzumab Switch CAMMS323/03409 (Pre Alemtuzumab)	IFNB-1a/Alemtuzumab Switch CAMMS323/03409 (Post Alemtuzumab)	IFNB-1a/Alemtuzumab Switch CAMMS324/03409 (Pre Alemtuzumab)	IFNB-1a/Alemtuzumab Switch CAMMS324/03409 (Post Alemtuzumab)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	139	139	143	143
Units: units on a scale				
arithmetic mean (confidence interval 95%)				
Change at Year 1	2.88 (0.49 to 5.27)	1.98 (-0.46 to 4.43)	1.83 (0.3 to 3.36)	1.21 (-0.31 to 2.74)
Change at Year 2	2.32 (-0.11 to 4.74)	2.08 (-0.38 to 4.54)	1.65 (0.05 to 3.25)	1.65 (-0.01 to 3.31)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Self-reported Quality of Life as Assessed by Functional Assessment of Multiple Sclerosis (FAMS) Score at Year 3, 4, 5 and 6

End point title	Change From Baseline in Self-reported Quality of Life as Assessed by Functional Assessment of Multiple Sclerosis (FAMS) Score at Year 3, 4, 5 and 6
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End point description:

FAMS comprised 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). Subjects provided their response based on the recall of past week. Each item was rated on a 5-point scale ranges from 0 (poor) to 4 (best), where higher scores indicated higher/better quality of life. Scores from 44 calculable items were

summed to provide FAMS total score. FAMS total score ranges from 0 (poor) to 176 (best), where higher scores indicated higher/better quality of life. Subset of full analysis set (FAS - defined as all subjects randomised in CAMMS223, CAMMS323, and CAMMS324 and who received at least 1 dose of study drug) included subjects who had received at least 1 dose of alemtuzumab in CAMMS323 and CAMMS324. Number of subjects analysed = subjects with available data for this endpoint.

End point type	Secondary
End point timeframe:	
Baseline (Month 0 of CAMMS323 and Month 0 of CAMMS324 for "Alemtuzumab Treatment CAMMS323 Extension" group and "Alemtuzumab Treatment CAMMS324 Extension" group, respectively), Year 3, 4, 5, 6	

End point values	Alemtuzumab Treatment CAMMS323 Extension	Alemtuzumab Treatment CAMMS324 Extension		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	340	372		
Units: units on a scale				
arithmetic mean (confidence interval 95%)				
Change at Year 3	5.28 (2.03 to 8.52)	4.55 (1.89 to 7.21)		
Change at Year 4	6.81 (3.55 to 10.08)	3.65 (0.98 to 6.32)		
Change at Year 5	4.82 (1.55 to 8.1)	3.57 (0.78 to 6.37)		
Change at Year 6	4.4 (1.03 to 7.78)	3.16 (0.07 to 6.25)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Self-reported Quality of Life as Assessed by Functional Assessment of Multiple Sclerosis (FAMS) Score Before and After Alemtuzumab Treatment: 2 Year Comparison

End point title	Change From Baseline in Self-reported Quality of Life as Assessed by Functional Assessment of Multiple Sclerosis (FAMS) Score Before and After Alemtuzumab Treatment: 2 Year Comparison
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End point description:

FAMS comprised 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). Subjects provided their response based on the recall of past week. Each item was rated on a 5-point scale ranges from 0 (poor) to 4 (best), where higher scores indicated higher/better quality of life. Scores from 44 calculable items were summed to provide FAMS total score. FAMS total score ranges from 0 (poor) to 176 (best), where higher scores indicated higher/better quality of life. The IFNB-1a/Alemtuzumab switch from CAMMS323 or CAMMS324 to CAMMS03409 pre alemtuzumab reporting group consisted of the same subjects as those in the corresponding post alemtuzumab reporting group. Subset of FAS who received IFNB-1a in CAMMS323 or CAMMS324 and who were treated with alemtuzumab in CAMMS03409.

End point type	Secondary
End point timeframe:	
Baseline (Year 0 of initial studies) up to Year 4	

End point values	IFNB-1a/Alemtuzumab Switch CAMMS323/03 409 (Pre Alemtuzumab)	IFNB-1a/Alemtuzumab Switch CAMMS323/03 409 (Post Alemtuzumab)	IFNB-1a/Alemtuzumab Switch CAMMS324/03 409 (Pre Alemtuzumab)	IFNB-1a/Alemtuzumab Switch CAMMS324/03 409 (Post Alemtuzumab)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	139	139	143	143
Units: units on a scale				
arithmetic mean (confidence interval 95%)				
Change at Year 1	4.27 (-1.17 to 9.72)	4.82 (0.1 to 9.53)	3.19 (-0.12 to 6.51)	5.83 (2.74 to 8.92)
Change at Year 2	1.88 (-3.63 to 7.38)	3.1 (-2.16 to 8.35)	0.93 (-2.86 to 4.71)	4.66 (1.07 to 8.24)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Quality of Life -5 Dimension (EQ-5D) Visual Analog Scale Score at Year 3, 4, 5 and 6

End point title	Change From Baseline in European Quality of Life -5 Dimension (EQ-5D) Visual Analog Scale Score at Year 3, 4, 5 and 6
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End point description:

EQ-5D is a standardized instrument for measuring health status and consisting of EQ-5D descriptive system and Visual Analogue Scale (VAS). EQ-5D descriptive system comprised of 5 dimensions of health: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension was measured on 3 levels (no problem, some problems and extreme problems). These 5-dimensional 3-level measurements were converted into single index utility score. Possible values for single index utility score ranged from -0.594 (severe problems in all dimensions) to 1.0 (no problem in all dimensions) on scale where 1 represented best possible health state. Subset of full analysis set (FAS - defined as all subjects randomised in CAMMS223, CAMMS323, and CAMMS324 and who received at least 1 dose of study drug) included subjects who had received at least 1 dose of alemtuzumab in CAMMS323 and CAMMS324. Number of subjects analysed = subjects with available data for this endpoint.

End point type	Secondary
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End point timeframe:

Baseline (Month 0 of CAMMS323 and Month 0 of CAMMS324 for "Alemtuzumab Treatment CAMMS323 Extension" group and "Alemtuzumab Treatment CAMMS324 Extension" group, respectively), Year 3, 4, 5 and 6

End point values	Alemtuzumab Treatment CAMMS323 Extension	Alemtuzumab Treatment CAMMS324 Extension		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	337	374		
Units: units on a scale				
arithmetic mean (confidence interval 95%)				

Change at Year 3	3.505 (1.438 to 5.572)	2.859 (1.008 to 4.71)		
Change at Year 4	5.144 (3.078 to 7.21)	2.992 (1.145 to 4.838)		
Change at Year 5	4.409 (2.303 to 6.515)	3.034 (1.169 to 4.898)		
Change at Year 6	4.134 (1.946 to 6.323)	3.155 (0.933 to 5.377)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Quality of Life -5 Dimension (EQ-5D) Visual Analog Scale Score Before and After Alemtuzumab Treatment: 2 Year Comparison

End point title	Change From Baseline in European Quality of Life -5 Dimension (EQ-5D) Visual Analog Scale Score Before and After Alemtuzumab Treatment: 2 Year Comparison
End point description:	EQ-5D is a standardized instrument for measuring health status and consisting of EQ-5D descriptive system and VAS. EQ-5D descriptive system comprised of 5 dimensions of health: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension was measured on 3 levels (no problem, some problems and extreme problems). These 5-dimensional 3-level measurements were converted into single index utility score. Possible values for single index utility score ranged from -0.594 (severe problems in all dimensions) to 1.0 (no problem in all dimensions) on scale where 1 represented best possible health state. The IFNB-1a/Alemtuzumab switch from CAMMS323 or CAMMS324 to CAMMS03409 pre alemtuzumab reporting group consisted of the same subjects as those in the corresponding post alemtuzumab reporting group. Subset of FAS who received IFNB-1a in CAMMS323 or CAMMS324 and who were treated with alemtuzumab in CAMMS03409.
End point type	Secondary
End point timeframe:	Baseline (Year 0 of initial studies) up to Year 4

End point values	IFNB-1a/Alemtuzumab Switch CAMMS323/03409 (Pre Alemtuzumab)	IFNB-1a/Alemtuzumab Switch CAMMS323/03409 (Post Alemtuzumab)	IFNB-1a/Alemtuzumab Switch CAMMS324/03409 (Pre Alemtuzumab)	IFNB-1a/Alemtuzumab Switch CAMMS324/03409 (Post Alemtuzumab)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	139	139	143	143
Units: units on scale				
arithmetic mean (confidence interval 95%)				
Change at Year 1	4.165 (0.639 to 7.691)	4.576 (1.419 to 7.733)	1.663 (-0.893 to 4.219)	4.337 (1.1614 to 7.059)
Change at Year 2	2.359 (-1.319 to 6.037)	4.515 (1.407 to 7.622)	-0.712 (-3.552 to 2.129)	3.346 (0.324 to 6.368)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AE) were collected from signature of the informed consent form in the extension study up to the end of extension study visit (up to Year 6) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported AEs are treatment-emergent adverse events (TEAEs), AEs that developed/worsened during or at any time after first alemtuzumab treatment. Alemtuzumab TEAEs were defined as AEs with start dates and start times on or after the date and time of the first alemtuzumab treatment in CAMMS03409 or in prior studies (CAMMS223, CAMMS323, or CAMMS324).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Alemtuzumab
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Reporting group description:

Subjects enrolled in any of the previous studies who had received alemtuzumab. Subjects enrolled in any of the previous studies who had received IFNB-1a, who received alemtuzumab 12 mg/day infusion in this study.

Serious adverse events	Alemtuzumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	376 / 1314 (28.61%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Anogenital Warts			
subjects affected / exposed	3 / 1314 (0.23%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
B-Cell Lymphoma			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Basal Cell Carcinoma			

subjects affected / exposed	1 / 1314 (0.08%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Benign Hydatidiform Mole				
subjects affected / exposed	1 / 1314 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Benign Neoplasm Of Thyroid Gland				
subjects affected / exposed	2 / 1314 (0.15%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Breast Cancer				
subjects affected / exposed	2 / 1314 (0.15%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Castleman's Disease				
subjects affected / exposed	1 / 1314 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cervix Carcinoma Stage Ii				
subjects affected / exposed	1 / 1314 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Insulinoma				
subjects affected / exposed	1 / 1314 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Invasive Ductal Breast Carcinoma				
subjects affected / exposed	1 / 1314 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Invasive Lobular Breast Carcinoma				

subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malignant Melanoma			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Meningioma Benign			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malignant Melanoma In Situ			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastatic Malignant Melanoma			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neoplasm Skin			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Non-Small Cell Lung Cancer			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Ovarian Adenoma			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Papillary Thyroid Cancer			

subjects affected / exposed	3 / 1314 (0.23%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Pancreatic Neuroendocrine Tumour			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Parathyroid Tumour Benign			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pituitary Tumour			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Squamous Cell Carcinoma			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thyroid Cancer			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Uterine Leiomyoma			
subjects affected / exposed	5 / 1314 (0.38%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Vulval Cancer Stage 0			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep Vein Thrombosis			

subjects affected / exposed	4 / 1314 (0.30%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Haematoma			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertension			
subjects affected / exposed	3 / 1314 (0.23%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Hypertensive Crisis			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Orthostatic Hypotension			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pallor			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral Arterial Occlusive Disease			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombophlebitis			

subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vasculitis			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Surgical and medical procedures			
Thyroidectomy			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Abortion Missed			
subjects affected / exposed	3 / 1314 (0.23%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Abortion			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Foetal Cardiac Disorder			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Foetal Death			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Foetal-Maternal Haemorrhage			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

<p>Hellp Syndrome</p> <p>subjects affected / exposed</p> <p>occurrences causally related to treatment / all</p> <p>deaths causally related to treatment / all</p>	<p>1 / 1314 (0.08%)</p> <p>0 / 1</p> <p>0 / 0</p>		
<p>Peripartum Cardiomyopathy</p> <p>subjects affected / exposed</p> <p>occurrences causally related to treatment / all</p> <p>deaths causally related to treatment / all</p>	<p>1 / 1314 (0.08%)</p> <p>0 / 1</p> <p>0 / 0</p>		
<p>Low Birth Weight Baby</p> <p>subjects affected / exposed</p> <p>occurrences causally related to treatment / all</p> <p>deaths causally related to treatment / all</p>	<p>1 / 1314 (0.08%)</p> <p>0 / 1</p> <p>0 / 0</p>		
<p>Placental Insufficiency</p> <p>subjects affected / exposed</p> <p>occurrences causally related to treatment / all</p> <p>deaths causally related to treatment / all</p>	<p>1 / 1314 (0.08%)</p> <p>0 / 1</p> <p>0 / 0</p>		
<p>Pre-Eclampsia</p> <p>subjects affected / exposed</p> <p>occurrences causally related to treatment / all</p> <p>deaths causally related to treatment / all</p>	<p>1 / 1314 (0.08%)</p> <p>0 / 1</p> <p>0 / 0</p>		
<p>Premature Separation Of Placenta</p> <p>subjects affected / exposed</p> <p>occurrences causally related to treatment / all</p> <p>deaths causally related to treatment / all</p>	<p>2 / 1314 (0.15%)</p> <p>0 / 2</p> <p>0 / 0</p>		
<p>General disorders and administration site conditions</p> <p>Catheter Site Pain</p> <p>subjects affected / exposed</p> <p>occurrences causally related to treatment / all</p> <p>deaths causally related to treatment / all</p>	<p>1 / 1314 (0.08%)</p> <p>0 / 1</p> <p>0 / 0</p>		
<p>Chest Pain</p> <p>subjects affected / exposed</p> <p>occurrences causally related to treatment / all</p> <p>deaths causally related to treatment / all</p>	<p>1 / 1314 (0.08%)</p> <p>0 / 1</p> <p>0 / 0</p>		

Chills				
subjects affected / exposed	1 / 1314 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Death				
subjects affected / exposed	1 / 1314 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Device Dislocation				
subjects affected / exposed	1 / 1314 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fatigue				
subjects affected / exposed	1 / 1314 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Inflammation				
subjects affected / exposed	1 / 1314 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Non-Cardiac Chest Pain				
subjects affected / exposed	2 / 1314 (0.15%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Perforated Ulcer				
subjects affected / exposed	1 / 1314 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	2 / 1314 (0.15%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				

Anaphylactoid Reaction			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Drug Hypersensitivity			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypersensitivity			
subjects affected / exposed	3 / 1314 (0.23%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Adnexa Uteri Mass			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cervical Dysplasia			
subjects affected / exposed	4 / 1314 (0.30%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Cystocele			
subjects affected / exposed	2 / 1314 (0.15%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Endometrial Hyperplasia			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endometriosis			
subjects affected / exposed	2 / 1314 (0.15%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Menometrorrhagia				
subjects affected / exposed	1 / 1314 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Menorrhagia				
subjects affected / exposed	2 / 1314 (0.15%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Ovarian Cyst				
subjects affected / exposed	6 / 1314 (0.46%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Ovarian Haemorrhage				
subjects affected / exposed	1 / 1314 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Parovarian Cyst				
subjects affected / exposed	1 / 1314 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pelvic Adhesions				
subjects affected / exposed	1 / 1314 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rectocele				
subjects affected / exposed	2 / 1314 (0.15%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Vaginal Haemorrhage				
subjects affected / exposed	2 / 1314 (0.15%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Vulvar Dysplasia				

subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute Respiratory Distress Syndrome			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Apnoea Neonatal			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Asthma			
subjects affected / exposed	2 / 1314 (0.15%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Bronchospasm			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	3 / 1314 (0.23%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Eosinophilic Pneumonia			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hiccups			

subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Interstitial Lung Disease			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural Effusion			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleurisy			
subjects affected / exposed	2 / 1314 (0.15%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pneumonia Aspiration			
subjects affected / exposed	2 / 1314 (0.15%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Pneumonitis			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumothorax Spontaneous			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary Embolism			
subjects affected / exposed	2 / 1314 (0.15%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Sleep Apnoea Syndrome			

subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory Failure			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Adjustment Disorder			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Affective Disorder			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bipolar Ii Disorder			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Completed Suicide			
subjects affected / exposed	2 / 1314 (0.15%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Depression			
subjects affected / exposed	2 / 1314 (0.15%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypomania			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Insomnia			

subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Major Depression			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mental Status Changes			
subjects affected / exposed	4 / 1314 (0.30%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Psychogenic Pain Disorder			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post-Traumatic Amnestic Disorder			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychogenic Tremor			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychotic Disorder			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Schizoaffective Disorder Bipolar Type			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Self Injurious Behaviour			

subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Suicide Attempt			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Suicidal Ideation			
subjects affected / exposed	6 / 1314 (0.46%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Biliary Dyskinesia			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholangitis			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholecystitis			
subjects affected / exposed	4 / 1314 (0.30%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Cholecystitis Acute			
subjects affected / exposed	2 / 1314 (0.15%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	4 / 1314 (0.30%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Hepatitis Acute			

subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sphincter Of Oddi Dysfunction			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Blood Creatinine Increased			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urine Ketone Body Present			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Accidental Overdose			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ankle Fracture			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cartilage Injury			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cervical Vertebral Fracture			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Concussion				
subjects affected / exposed	3 / 1314 (0.23%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Contusion				
subjects affected / exposed	2 / 1314 (0.15%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Femur Fracture				
subjects affected / exposed	1 / 1314 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fibula Fracture				
subjects affected / exposed	2 / 1314 (0.15%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Gastrostomy Failure				
subjects affected / exposed	1 / 1314 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hip Fracture				
subjects affected / exposed	1 / 1314 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Humerus Fracture				
subjects affected / exposed	1 / 1314 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Incision Site Oedema				
subjects affected / exposed	1 / 1314 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intentional Overdose				

subjects affected / exposed	2 / 1314 (0.15%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Laceration			
subjects affected / exposed	2 / 1314 (0.15%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Ligament Sprain			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Meniscus Injury			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lumbar Vertebral Fracture			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Multiple Fractures			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Overdose			
subjects affected / exposed	2 / 1314 (0.15%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pancreatic Injury			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pelvic Fracture			

subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post Lumbar Puncture Syndrome			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post Procedural Fistula			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post Procedural Haematoma			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Procedural Nausea			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Procedural Pain			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skull Fractured Base			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal Column Injury			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Splenic Rupture			

subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Subdural Haematoma			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tibia Fracture			
subjects affected / exposed	2 / 1314 (0.15%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Ulna Fracture			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wound			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wound Dehiscence			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wrist Fracture			
subjects affected / exposed	2 / 1314 (0.15%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Foetal Cystic Hygroma			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			

Acute Myocardial Infarction				
subjects affected / exposed	3 / 1314 (0.23%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Angina Pectoris				
subjects affected / exposed	4 / 1314 (0.30%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Atrial Fibrillation				
subjects affected / exposed	1 / 1314 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bradycardia				
subjects affected / exposed	2 / 1314 (0.15%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Bradycardia Foetal				
subjects affected / exposed	1 / 1314 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bradycardia Neonatal				
subjects affected / exposed	1 / 1314 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bundle Branch Block Right				
subjects affected / exposed	1 / 1314 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac Arrest				
subjects affected / exposed	1 / 1314 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac Failure Congestive				

subjects affected / exposed	2 / 1314 (0.15%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Congestive Cardiomyopathy			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myocardial Infarction			
subjects affected / exposed	2 / 1314 (0.15%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pericarditis			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sinus Bradycardia			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tachycardia			
subjects affected / exposed	3 / 1314 (0.23%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Altered State Of Consciousness			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Basal Ganglia Haemorrhage			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebral Haemorrhage			

subjects affected / exposed	2 / 1314 (0.15%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Complex Partial Seizures			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Depressed Level Of Consciousness			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dizziness			
subjects affected / exposed	2 / 1314 (0.15%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Dysarthria			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Embolic Stroke			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	7 / 1314 (0.53%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		
Intracranial Aneurysm			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intraventricular Haemorrhage			

subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Loss Of Consciousness			
subjects affected / exposed	2 / 1314 (0.15%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Migraine			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Multiple Sclerosis			
subjects affected / exposed	4 / 1314 (0.30%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Multiple Sclerosis Relapse			
subjects affected / exposed	67 / 1314 (5.10%)		
occurrences causally related to treatment / all	0 / 115		
deaths causally related to treatment / all	0 / 0		
Optic Neuritis			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	4 / 1314 (0.30%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Status Epilepticus			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Syncope			

subjects affected / exposed	9 / 1314 (0.68%)		
occurrences causally related to treatment / all	0 / 9		
deaths causally related to treatment / all	0 / 0		
Tension Headache			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tremor			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Trigeminal Neuralgia			
subjects affected / exposed	3 / 1314 (0.23%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Uhthoff's Phenomenon			
subjects affected / exposed	6 / 1314 (0.46%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Acquired Haemophilia			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Anaemia			
subjects affected / exposed	3 / 1314 (0.23%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Autoimmune Haemolytic Anaemia			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Autoimmune Pancytopenia			

subjects affected / exposed	1 / 1314 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Febrile Neutropenia				
subjects affected / exposed	1 / 1314 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemolytic Anaemia				
subjects affected / exposed	2 / 1314 (0.15%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Haemorrhagic Anaemia				
subjects affected / exposed	1 / 1314 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Immune Thrombocytopenic Purpura				
subjects affected / exposed	16 / 1314 (1.22%)			
occurrences causally related to treatment / all	0 / 17			
deaths causally related to treatment / all	0 / 0			
Lymphadenopathy				
subjects affected / exposed	1 / 1314 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	1 / 1314 (0.08%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Pancytopenia				
subjects affected / exposed	1 / 1314 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				

subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Cataract			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine Ophthalmopathy			
subjects affected / exposed	4 / 1314 (0.30%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Glaucoma			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Iridocyclitis			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Optic Atrophy			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vision Blurred			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			

Abdominal Distension				
subjects affected / exposed	1 / 1314 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal Hernia				
subjects affected / exposed	1 / 1314 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal Pain				
subjects affected / exposed	11 / 1314 (0.84%)			
occurrences causally related to treatment / all	0 / 11			
deaths causally related to treatment / all	0 / 0			
Abdominal Pain Upper				
subjects affected / exposed	1 / 1314 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ascites				
subjects affected / exposed	1 / 1314 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Colitis				
subjects affected / exposed	3 / 1314 (0.23%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Colitis Ischaemic				
subjects affected / exposed	1 / 1314 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	1 / 1314 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				

subjects affected / exposed	3 / 1314 (0.23%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Duodenitis			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Enteritis			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Faecaloma			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastric Ulcer Haemorrhage			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastritis			
subjects affected / exposed	2 / 1314 (0.15%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Impaired Gastric Emptying			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Inguinal Hernia			
subjects affected / exposed	2 / 1314 (0.15%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Nausea			

subjects affected / exposed	7 / 1314 (0.53%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		
Oesophagitis			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatic Fistula			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatic Pseudocyst			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis Acute			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peptic Ulcer			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Small Intestinal Obstruction			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper Gastrointestinal Haemorrhage			

subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	6 / 1314 (0.46%)		
occurrences causally related to treatment / all	0 / 9		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Erythema Nodosum			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperhidrosis			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Polymorphic Eruption Of Pregnancy			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rash			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rash Generalised			
subjects affected / exposed	2 / 1314 (0.15%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Skin Ulcer			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urticaria			

subjects affected / exposed	2 / 1314 (0.15%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	2 / 1314 (0.15%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Automatic Bladder			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Calculus Bladder			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Calculus Ureteric			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Glomerulonephritis			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Glomerulonephritis Membranous			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haematuria			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nephrolithiasis			

subjects affected / exposed	4 / 1314 (0.30%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Renal Colic			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal Failure			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal Mass			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal Tubular Necrosis			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary Retention			
subjects affected / exposed	4 / 1314 (0.30%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Autoimmune Hypothyroidism			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Autoimmune Thyroiditis			
subjects affected / exposed	4 / 1314 (0.30%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Basedow's Disease			

subjects affected / exposed	39 / 1314 (2.97%)		
occurrences causally related to treatment / all	0 / 40		
deaths causally related to treatment / all	0 / 0		
Goitre			
subjects affected / exposed	3 / 1314 (0.23%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Hyperparathyroidism			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperthyroidism			
subjects affected / exposed	14 / 1314 (1.07%)		
occurrences causally related to treatment / all	0 / 14		
deaths causally related to treatment / all	0 / 0		
Hypothyroidism			
subjects affected / exposed	4 / 1314 (0.30%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 1314 (0.15%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Arthritis			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Back Disorder			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Back Pain			

subjects affected / exposed	2 / 1314 (0.15%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Chondropathy			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Costochondritis			
subjects affected / exposed	2 / 1314 (0.15%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Flank Pain			
subjects affected / exposed	2 / 1314 (0.15%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Haemarthrosis			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Joint Effusion			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Joint Instability			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Joint Range Of Motion Decreased			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Muscle Spasms			

subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Muscular Weakness			
subjects affected / exposed	2 / 1314 (0.15%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal Chest Pain			
subjects affected / exposed	2 / 1314 (0.15%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal Stiffness			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			
subjects affected / exposed	2 / 1314 (0.15%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Osteonecrosis			
subjects affected / exposed	2 / 1314 (0.15%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pain In Jaw			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Plantar Fasciitis			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rotator Cuff Syndrome			

subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sapho Syndrome			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal Pain			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Temporomandibular Joint Syndrome			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abscess Bacterial			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abscess Limb			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Appendicitis			
subjects affected / exposed	2 / 1314 (0.15%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Appendicitis Perforated			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bone Abscess			

subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Breast Abscess			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	6 / 1314 (0.46%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Chronic Hepatitis C			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device Related Infection			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			
subjects affected / exposed	2 / 1314 (0.15%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Escherichia Urinary Tract Infection			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endometritis			

subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	7 / 1314 (0.53%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		
Furuncle			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis Bacterial			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis Viral			
subjects affected / exposed	2 / 1314 (0.15%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Helicobacter Infection			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Herpes Zoster			
subjects affected / exposed	10 / 1314 (0.76%)		
occurrences causally related to treatment / all	0 / 12		
deaths causally related to treatment / all	0 / 0		
Hiv Infection			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infectious Colitis			

subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infective Myositis			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	2 / 1314 (0.15%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Lower Respiratory Tract Infection			
subjects affected / exposed	2 / 1314 (0.15%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Lung Abscess			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreas Infection			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oral Herpes			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			

subjects affected / exposed	13 / 1314 (0.99%)		
occurrences causally related to treatment / all	0 / 13		
deaths causally related to treatment / all	0 / 0		
Pneumonia Fungal			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia Legionella			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post Procedural Infection			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary Tuberculosis			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	4 / 1314 (0.30%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis Acute			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory Tract Infection Viral			
subjects affected / exposed	2 / 1314 (0.15%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Scrotal Abscess			

subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	8 / 1314 (0.61%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 1		
Soft Tissue Infection			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Staphylococcal Abscess			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Subcutaneous Abscess			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tracheobronchitis			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tubo-Ovarian Abscess			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary Tract Infection			
subjects affected / exposed	7 / 1314 (0.53%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 0		
Urosepsis			

subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Varicella Zoster Virus Infection			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Viral Infection			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	6 / 1314 (0.46%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Diabetic Ketoacidosis			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Electrolyte Imbalance			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypocalcaemia			
subjects affected / exposed	2 / 1314 (0.15%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			

subjects affected / exposed	2 / 1314 (0.15%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypophosphataemia			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malnutrition			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Obesity			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Type 1 Diabetes Mellitus			
subjects affected / exposed	1 / 1314 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Alemtuzumab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1225 / 1314 (93.23%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	92 / 1314 (7.00%)		
occurrences (all)	109		
Flushing			
subjects affected / exposed	79 / 1314 (6.01%)		
occurrences (all)	119		
General disorders and administration site conditions			

Pain			
subjects affected / exposed	85 / 1314 (6.47%)		
occurrences (all)	120		
Fatigue			
subjects affected / exposed	280 / 1314 (21.31%)		
occurrences (all)	357		
Pyrexia			
subjects affected / exposed	228 / 1314 (17.35%)		
occurrences (all)	318		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	127 / 1314 (9.67%)		
occurrences (all)	168		
Oropharyngeal Pain			
subjects affected / exposed	91 / 1314 (6.93%)		
occurrences (all)	116		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	133 / 1314 (10.12%)		
occurrences (all)	150		
Depression			
subjects affected / exposed	154 / 1314 (11.72%)		
occurrences (all)	180		
Insomnia			
subjects affected / exposed	231 / 1314 (17.58%)		
occurrences (all)	278		
Investigations			
Blood Creatinine Increased			
subjects affected / exposed	68 / 1314 (5.18%)		
occurrences (all)	85		
Protein Urine Present			
subjects affected / exposed	78 / 1314 (5.94%)		
occurrences (all)	135		
Injury, poisoning and procedural complications			

Contusion subjects affected / exposed occurrences (all)	141 / 1314 (10.73%) 322		
Fall subjects affected / exposed occurrences (all)	87 / 1314 (6.62%) 244		
Cardiac disorders Tachycardia subjects affected / exposed occurrences (all)	86 / 1314 (6.54%) 114		
Nervous system disorders Hypoaesthesia subjects affected / exposed occurrences (all)	176 / 1314 (13.39%) 299		
Dizziness subjects affected / exposed occurrences (all)	130 / 1314 (9.89%) 168		
Headache subjects affected / exposed occurrences (all)	437 / 1314 (33.26%) 783		
Multiple Sclerosis subjects affected / exposed occurrences (all)	70 / 1314 (5.33%) 82		
Multiple Sclerosis Relapse subjects affected / exposed occurrences (all)	508 / 1314 (38.66%) 947		
Paraesthesia subjects affected / exposed occurrences (all)	168 / 1314 (12.79%) 260		
Eye disorders Vision Blurred subjects affected / exposed occurrences (all)	75 / 1314 (5.71%) 94		
Gastrointestinal disorders			

Abdominal Pain			
subjects affected / exposed	72 / 1314 (5.48%)		
occurrences (all)	87		
Diarrhoea			
subjects affected / exposed	170 / 1314 (12.94%)		
occurrences (all)	234		
Constipation			
subjects affected / exposed	104 / 1314 (7.91%)		
occurrences (all)	125		
Dyspepsia			
subjects affected / exposed	71 / 1314 (5.40%)		
occurrences (all)	83		
Nausea			
subjects affected / exposed	206 / 1314 (15.68%)		
occurrences (all)	323		
Vomiting			
subjects affected / exposed	130 / 1314 (9.89%)		
occurrences (all)	182		
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	96 / 1314 (7.31%)		
occurrences (all)	135		
Rash Generalised			
subjects affected / exposed	110 / 1314 (8.37%)		
occurrences (all)	173		
Rash			
subjects affected / exposed	208 / 1314 (15.83%)		
occurrences (all)	333		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	92 / 1314 (7.00%)		
occurrences (all)	217		
Proteinuria			
subjects affected / exposed	122 / 1314 (9.28%)		
occurrences (all)	239		
Endocrine disorders			

Autoimmune Thyroiditis subjects affected / exposed occurrences (all)	67 / 1314 (5.10%) 67		
Basedow's Disease subjects affected / exposed occurrences (all)	165 / 1314 (12.56%) 170		
Hyperthyroidism subjects affected / exposed occurrences (all)	142 / 1314 (10.81%) 158		
Hypothyroidism subjects affected / exposed occurrences (all)	140 / 1314 (10.65%) 151		
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	216 / 1314 (16.44%) 300		
Back Pain subjects affected / exposed occurrences (all)	205 / 1314 (15.60%) 262		
Muscle Spasms subjects affected / exposed occurrences (all)	132 / 1314 (10.05%) 182		
Muscular Weakness subjects affected / exposed occurrences (all)	113 / 1314 (8.60%) 167		
Musculoskeletal Pain subjects affected / exposed occurrences (all)	75 / 1314 (5.71%) 87		
Myalgia subjects affected / exposed occurrences (all)	80 / 1314 (6.09%) 96		
Pain In Extremity subjects affected / exposed occurrences (all)	189 / 1314 (14.38%) 320		

Infections and infestations Gastroenteritis subjects affected / exposed occurrences (all) Bronchitis subjects affected / exposed occurrences (all)	81 / 1314 (6.16%) 100 133 / 1314 (10.12%) 199		
Gastroenteritis Viral subjects affected / exposed occurrences (all) Herpes Zoster subjects affected / exposed occurrences (all) Oral Herpes subjects affected / exposed occurrences (all) Influenza subjects affected / exposed occurrences (all)	85 / 1314 (6.47%) 112 123 / 1314 (9.36%) 145 78 / 1314 (5.94%) 147 155 / 1314 (11.80%) 195		
Nasopharyngitis subjects affected / exposed occurrences (all)	382 / 1314 (29.07%) 949		
Upper Respiratory Tract Infection subjects affected / exposed occurrences (all)	272 / 1314 (20.70%) 501		
Sinusitis subjects affected / exposed occurrences (all)	186 / 1314 (14.16%) 322		
Pharyngitis subjects affected / exposed occurrences (all)	68 / 1314 (5.18%) 86		
Urinary Tract Infection subjects affected / exposed occurrences (all)	360 / 1314 (27.40%) 938		
Metabolism and nutrition disorders			

Vitamin D Deficiency subjects affected / exposed occurrences (all)	83 / 1314 (6.32%) 85		
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More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 February 2010	<ul style="list-style-type: none">Allowed use of disease modifying therapies including follow-up.Revision to allow female subjects to become pregnant 6 months after infusion.Addition of substudy to evaluate effect of alemtuzumab on cardiac repolarization via QT assessments.Allowed one-time blood sample collection for future genotyping.
26 August 2010	<ul style="list-style-type: none">Addition of one time point for a PK sample and triplicate electrocardiogram (ECG) collection on study Day 6 or 8 in order to assess any potential delayed alemtuzumab effects on QT.
18 April 2012	<ul style="list-style-type: none">To extend study by 1 additional year; from 3 years (36 months) to 4 years (48 months).
26 June 2013	<ul style="list-style-type: none">Study extended to allow subjects to remain in the study through the time of drug approval or until long term care was available.Added collection of vital signs during alemtuzumab infusion.
20 June 2014	<ul style="list-style-type: none">Medical events of interest (MEOI) table revised to list specific examples and reporting times.To specify that an enrolled subject could remain in the Extension Study for a minimum of 48 months from study entryTo specify assessment of rater blinding to include annual visits after 24 months.Clarification of ITP (immune thrombocytopenic purpura) and anti-glomerular basement membrane (GBM) surveillance monitoring.To revise that last completion of CARE-MS monthly monitoring survey occurred at the end of the study.Added Section 9.4.19 to define symptomatic overdose with Investigational Medicinal Product.Duration of the study was extended to allow subjects in the United States to remain on the study until a follow-up study was available or through Month 72, whichever occurred first.MEOI table revised to list specific examples and reporting times.Revised number of Months (from 59 to 71) that subjects would have to qualify and receive treatment after enrollment.Protocol updated throughout to add monthly visits for Months 61 through 71, accordingly.Clarification of ITP and Anti-GBM surveillance monitoring.Revised Section 9.4.19 to clarify symptomatic overdose with IMP.Revised that last completion of CARE-MS monthly monitoring survey occurred at the end of the study.Specified assessment of rater blinding to be done at Month 72 visit.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/18946064>

<http://www.ncbi.nlm.nih.gov/pubmed/16044212>