Clinical trial results:
An Open-Label, Multicenter, Extension Study to Evaluate the Safety and Tolerability of Natalizumab Following Re-Initiation of Dosing in Multiple Sclerosis Subjects Who Have Completed Study C-1801, C-1802, C-1803, or C-1808 and a Dosing Suspension Safety Evaluation

Summary

EudraCT number	2005-004061-41
Trial protocol	GB BE FI IE DE AT SE HU DK CZ ES IT GR
Global end of trial date	30 April 2014

Results information

Result version number	v1 (current)
This version publication date	04 February 2016
First version publication date	07 May 2015

Trial information

Trial identification

Sponsor protocol code	101-MS-321

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00297232
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Biogen
Sponsor organisation address	225 Binney Street, Cambridge, United States, 02142
Public contact	Biogen Study Medical Director, Biogen, clinicaltrials@biogen.com
Scientific contact	Biogen Study Medical Director, Biogen, clinicaltrials@biogen.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	30 April 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 April 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives for the initial treatment period of this study are to further evaluate the safety of natalizumab monotherapy by evaluating the risk of hypersensitivity reactions and immunogenicity following re-exposure to natalizumab and confirming the safety of switching from interferon (IFN), glatiramer acetate, or other multiple sclerosis (MS) therapies to natalizumab. The primary objective for the long-term treatment period of this study is to evaluate the long-term impact of natalizumab monotherapy on the progression of disability measured by Expanded Disability Status Scale (EDSS) changes over time.

Protection of trial subjects:

All infusions were to be administered in a clinic setting to allow for safety monitoring. Subjects were to remain in the clinic for 1 hour postinfusion for observation. An anti-natalizumab antibody sample was to be collected if an allergic reaction to natalizumab was suspected. If a subject was unable to tolerate the natalizumab dose of 300 mg intravenous (IV), the infusion was to be terminated immediately and the subject was to be discontinued from the study after follow-up procedures had been completed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 March 2006
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	Spain: 31
Country: Number of subjects enrolled	Sweden: 23
Country: Number of subjects enrolled	United Kingdom: 72
Country: Number of subjects enrolled	Belgium: 19
Country: Number of subjects enrolled	Czech Republic: 107
Country: Number of subjects enrolled	Denmark: 9
Country: Number of subjects enrolled	Finland: 10
Country: Number of subjects enrolled	France: 64
Country: Number of subjects enrolled	Germany: 22
Country: Number of subjects enrolled	Greece: 4
Country: Number of subjects enrolled	Hungary: 47
Country: Number of subjects enrolled	Ireland: 8
Country: Number of subjects enrolled	Italy: 16
Country: Number of subjects enrolled	Poland: 122

Country: Number of subjects enrolled	Netherlands: 52
Country: Number of subjects enrolled	Canada: 49
Country: Number of subjects enrolled	Turkey: 29
Country: Number of subjects enrolled	Australia: 24
Country: Number of subjects enrolled	United States: 356
Country: Number of subjects enrolled	Switzerland: 11
Country: Number of subjects enrolled	Israel: 10
Country: Number of subjects enrolled	New Zealand: 9
Worldwide total number of subjects	1094
EEA total number of subjects	606

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)	1094
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study 101-MS-321 (2005-004061-41) was initiated for subjects in Europe and the rest of the world in parallel with 101-MS-322 (NCT00306592) in North America. After 48 weeks, subjects from 101-MS-322 could enter 101-MS-321, considered the Long-Term Treatment period of 101-MS-322. The primary purpose and primary outcome for both studies are identical.

Pre-assignment

Screening details:

Subjects from studies 101-MS-321 (2005-004061-41) and 101-MS-322 (NCT00306592) are included in this presentation of combined final data.

Period 1

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

Arms

Arm title	Natalizumab

Arm description:

300 mg IV infusions once every 4 weeks for up to 480 weeks

Arm type	Experimental
Investigational medicinal product name	Natalizumab
Investigational medicinal product code	BG00002
Other name	Recombinant humanized anti-alpha 4 integrin antibody
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Study site staff were to refer to the Directions for Handling and Administration for specific instructions on the handling and administration of natalizumab.

Number of subjects in period 1	Natalizumab
Started	1094
Completed	489
Not completed	605
Disease progression	8
No data available after Week 264	161
Miscellaneous	5
Adverse event	63
Investigator withdrew from program	19
Anti-John Cunninghan Virus Antibody Positive	13
Subject was noncompliant	9
Sponsor decision	34

Persistently positive antibodies	11
Consent withdrawn by subject	37
Switched to Commercial Tysabri	22
Death	9
Unknown	1
Subject relocated	7
Did Not Enroll to Week 480	17
Lost to follow-up	10
Anti-natalizumab positive	8
Voluntary withdrawal	120
Fear of progressive multifocal leukoencephalopathy	10
Lack of efficacy	7
Did Not Enroll to Week 264	34

Baseline characteristics

Reporting groups	
Reporting group title	Natalizumab

Reporting group description: -

Reporting group values	Natalizumab	Total	
Number of subjects	1094	1094	
Age categorical Units: Subjects			
20 to 29 years	98	98	
30 to 39 years	347	347	
40 to 49 years	454	454	
50 to 59 years	195	195	
Age continuous Units: years			
arithmetic mean	41.4		
standard deviation	± 8.12	-	
Gender categorical Units: Subjects			
Female	755	755	
Male	339	339	

End points

End points reporting groups

Reporting group title	Natalizumab

Reporting group description:

300 mg IV infusions once every 4 weeks for up to 480 weeks

Primary: Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious AEs (SAEs) to Week 48

End point title	Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious AEs (SAEs) to Week 48[1]

End point description:

AEs: any sign, symptom, or diagnosis/disease that is unfavorable or unintended, that is new, or if pre-existing, worsens in subjects administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. SAEs: an event that results in death; an event that, in the view of the investigator, places the subject at immediate risk of death (a life-threatening event); an outcome that results in a congenital anomaly/birth defect diagnosed in a child of a subject; an event that requires or prolongs inpatient hospitalization; an event that results in persistent or significant disability/incapacity. Any other medically important event that, in the opinion of the investigator, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Treatment-emergent AEs: events in subjects who had received at least 1 dose of study drug, regardless of relationship to study drug.

End point type	Primary

End point timeframe:

Baseline through Week 48

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: Descriptive data for this endpoint was collected and is presented here, per protocol.

End point values	Natalizumab			
Subject group type	Reporting group			
Number of subjects analysed	1094[2]			
Units: subjects				
AE	826			
Moderate or severe AE	487			
Severe AE	66			
AE related to study drug	161			
SAE	61			
SAE related to study drug	5			
Discontinuation of study drug due to AE	24			
Withdrawal from study due to AE	24			

Notes:

[2] - subjects receiving at least 1 dose of study drug

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Hypersensitivity-related Adverse Events to Week 48

End point title	Number of Subjects with Hypersensitivity-related Adverse Events to Week 48[3]

End point description:

For purposes of this analysis, the terms 'hypersensitivity' and 'drug hypersensitivity' were categorized by their temporal relationship to study drug infusion (within 2 hours of the start of the infusion), and were considered equivalent. Hypersensitivity reactions are defined as infusion reactions with the following preferred terms: hypersensitivity not otherwise specified (NOS), anaphylactic reaction, anaphylactoid reaction, dermatitis allergic, drug hypersensitivity, urticaria NOS, vasoconstriction, urticaria generalised, hypersensitivity, urticaria.

End point type	Primary

End point timeframe:

Baseline to Week 48

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: Descriptive data for this endpoint was collected and is presented here, per protocol.

End point values	Natalizumab			
Subject group type	Reporting group			
Number of subjects analysed	1094[4]			
Units: subjects	8			

Notes:

[4] - subjects receiving at least 1 dose of study drug

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Antibodies to Natalizumab to Week 24

End point title	Number of Subjects with Antibodies to Natalizumab to Week

End point description:

'Positive with unknown persistence' is defined as a positive result (≥0.5 micrograms/mL) at one timepoint only with no confirmatory re-test available at least 42 days later. 'Transient positive' is defined as a positive at one timepoint but negative upon re-test at least 42 days later. 'Persistent positive' is defined as positive at 2 or more timepoints separated by at least 42 days. The threshold for classifying a sample as 'antibody positive' was set at the lowest level of reactivity that had a measurable impact on drug serum concentrations.

End point type	Primary

End point timeframe:

Baseline (Week 0), Week 4, Week 24 (test was repeated after 8 weeks if positive, to confirm persistence)

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: Descriptive data for this endpoint was collected and is presented here, per protocol.

End point values	Natalizumab			
Subject group type	Reporting group			
Number of subjects analysed	1043[6]			
Units: subjects				
Antibody negative	1004			
Antibody positive with unknown persistence	15			
Antibody transient positive	8			

Antibody persistent positive	16			

Notes:

[6] - subjects with a negative baseline antibody result and ≥ 1 antibody result after the first dose

Statistical analyses

No statistical analyses for this end point

Primary: Time to 24-week Confirmed Expanded Disability Status Scale (EDSS) Progression

End point title	Time to 24-week Confirmed Expanded Disability Status Scale (EDSS) Progression[7]

End point description:

Time to 24-week confirmed EDSS progression in subjects with at least 2 post-baseline milestone EDSS assessments. EDSS assesses disability in 8 functional systems. An overall score ranging from 0 (normal) to 10 (death due to MS) was reported. Confirmed 24-week EDSS progression is defined as ≥ 0.5 point increase from a baseline EDSS ≥ 6.0, or ≥ 1.0 point increase from a baseline EDSS ≥ 1.0 and < 6.0, or ≥ 1.5 point increase from a baseline EDSS of 0, all sustained for 24 weeks.

End point type	Primary

End point timeframe:

up to 480 weeks

Notes:

[7] - 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: Descriptive data for this endpoint was collected and is presented here, per protocol.

End point values	Natalizumab			
Subject group type	Reporting group			
Number of subjects analysed	220[8]			
Units: weeks				
median (inter-quartile range (Q1-Q3))	121.9 (67.9 to 216.1)			

Notes:

[8] - subjects with EDSS progression (regardless of length of follow-up) sustained for 24 weeks

Statistical analyses

No statistical analyses for this end point

Primary: Time to 48-week Confirmed EDSS Progression

End point title	Time to 48-week Confirmed EDSS Progression[9]

End point description:

Time to 48-week confirmed EDSS progression in subjects with at least 2 post-baseline milestone EDSS assessments. EDSS assesses disability in 8 functional systems. An overall score ranging from 0 (normal) to 10 (death due to MS) was reported. Confirmed 48-week EDSS progression is defined as ≥ 0.5 point increase from a baseline EDSS ≥ 6.0, or ≥ 1.0 point increase from a baseline EDSS ≥ 1.0 and < 6.0, or ≥ 1.5 point increase from a baseline EDSS of 0, all sustained for 48 weeks.

End point type	Primary

End point timeframe:

up to 480 weeks

Notes:

[9] - 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: Descriptive data for this endpoint was collected and is presented here, per protocol.

End point values	Natalizumab			
Subject group type	Reporting group			
Number of subjects analysed	181[10]			
Units: weeks				
median (inter-quartile range (Q1-Q3))	130.1 (72.4 to 216.1)			

Notes:

[10] - subjects with EDSS progression (regardless of length of follow-up) sustained for 48 weeks

Statistical analyses

No statistical analyses for this end point

Primary: Time to 24-week Confirmed EDSS Improvement Where Baseline ≥ 2.0

End point title	Time to 24-week Confirmed EDSS Improvement Where Baseline ≥ 2.0[11]

End point description:

Time to 24-week confirmed EDSS improvement in subjects with at least 2 post-baseline milestone EDSS assessments. EDSS assesses disability in 8 functional systems. An overall score ranging from 0 (normal) to 10 (death due to MS) was reported. Confirmed 24-week EDSS improvement is defined as >=1.0 point decrease from baseline sustained for 24 weeks.

End point type	Primary

End point timeframe:

up to 480 weeks

Notes:

[11] - 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: Descriptive data for this endpoint was collected and is presented here, per protocol.

End point values	Natalizumab			
Subject group type	Reporting group			
Number of subjects analysed	173[12]			
Units: weeks				
median (inter-quartile range (Q1-Q3))	48.1 (24.1 to 119.9)			

Notes:

[12] - subjects with EDSS improvement (regardless of length of follow-up) sustained for 24 weeks

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious adverse events (SAEs) were collected from Screening through the follow-up (492 weeks). Non-serious AEs were collected from baseline through Week 264.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Natalizumab

Reporting group description:

300 mg IV infusions once every 4 weeks for up to 480 weeks

Serious adverse events	Natalizumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	231 / 1094 (21.12%)		
number of deaths (all causes)	11		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	5 / 1094 (0.46%)		
occurrences causally related to treatment / all	2 / 5		
deaths causally related to treatment / all	0 / 0		
Malignant melanoma			
subjects affected / exposed	5 / 1094 (0.46%)		
occurrences causally related to treatment / all	3 / 5		
deaths causally related to treatment / all	0 / 0		
Uterine leiomyoma			
subjects affected / exposed	5 / 1094 (0.46%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Intraductal proliferative breast lesion			

subjects affected / exposed	3 / 1094 (0.27%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Adenocarcinoma of salivary gland			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Bile duct adenocarcinoma			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Bladder transitional cell carcinoma			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebellopontine angle tumour			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colon cancer			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lobular breast carcinoma in situ			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung adenocarcinoma			

subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung neoplasm malignant				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	1 / 1			
Meningioma				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metastatic malignant melanoma				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Prostate cancer				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Teratoma				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Thyroid adenoma				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Breast cancer				
subjects affected / exposed	2 / 1094 (0.18%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Peripheral ischaemia				

subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombophlebitis			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Venous stenosis			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Deep vein thrombosis			
subjects affected / exposed	2 / 1094 (0.18%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Peripheral nerve decompression			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal laminectomy			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thyroid nodule removal			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular graft			
subjects affected / exposed	1 / 1094 (0.09%)		
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	2 / 1094 (0.18%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Abortion spontaneous				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Foetal death				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Haemorrhage in pregnancy				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Premature baby				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Pyrexia				
subjects affected / exposed	2 / 1094 (0.18%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Chest pain				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fatigue				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Multi-organ failure				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Oedema				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pain				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Polyp				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Immune reconstitution inflammatory syndrome				
subjects affected / exposed	11 / 1094 (1.01%)			
occurrences causally related to treatment / all	9 / 12			
deaths causally related to treatment / all	0 / 0			
Anaphylactic shock				
subjects affected / exposed	2 / 1094 (0.18%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Hypersensitivity				
subjects affected / exposed	2 / 1094 (0.18%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
Anaphylactic reaction				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Drug hypersensitivity				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Metrorrhagia				
subjects affected / exposed	2 / 1094 (0.18%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Uterine polyp				
subjects affected / exposed	2 / 1094 (0.18%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Adnexal torsion				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Breast hyperplasia				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Breast mass				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cervical dysplasia				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Menometrorrhagia				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Menorrhagia				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ovarian cyst				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Rectocele				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vaginal prolapse				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Nasal polyps				
subjects affected / exposed	2 / 1094 (0.18%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Aspiration				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Asthma				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Chronic obstructive pulmonary disease				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 1			

Obstructive airways disorder				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Psychiatric disorders				
Depression				
subjects affected / exposed	4 / 1094 (0.37%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Suicide attempt				
subjects affected / exposed	3 / 1094 (0.27%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Completed suicide				
subjects affected / exposed	2 / 1094 (0.18%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Mania				

subjects affected / exposed	2 / 1094 (0.18%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Suicidal ideation			
subjects affected / exposed	2 / 1094 (0.18%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Abnormal behaviour			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Anxiety disorder			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bipolar I disorder			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Confusional state			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Obsessive-compulsive disorder			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychotic disorder			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Schizophrenia			

subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Blood pressure increased			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Polyomavirus test positive			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	7 / 1094 (0.64%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		
Head injury			
subjects affected / exposed	4 / 1094 (0.37%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Lower limb fracture			
subjects affected / exposed	3 / 1094 (0.27%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Concussion			
subjects affected / exposed	2 / 1094 (0.18%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Facial bones fracture			
subjects affected / exposed	2 / 1094 (0.18%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Humerus fracture			
subjects affected / exposed	2 / 1094 (0.18%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Road traffic accident			
subjects affected / exposed	2 / 1094 (0.18%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Wrist fracture			
subjects affected / exposed	2 / 1094 (0.18%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Accidental overdose			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Animal bite			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ankle fracture			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Arteriovenous fistula site complication			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Arthropod bite			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Face injury			

subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Femur fracture				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fibula fracture				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Foot fracture				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gun shot wound				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hip fracture				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Laceration				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lumbar vertebral fracture				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Post procedural haemorrhage				

subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rib fracture			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tendon rupture			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Traumatic intracranial haemorrhage			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ulna fracture			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Congenital anomaly			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 1094 (0.18%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	2 / 1094 (0.18%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		

Angina pectoris				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Coronary artery occlusion				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Coronary artery stenosis				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myocardial fibrosis				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sinus tachycardia				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Multiple sclerosis relapse				
subjects affected / exposed	21 / 1094 (1.92%)			
occurrences causally related to treatment / all	0 / 24			
deaths causally related to treatment / all	0 / 0			
Multiple sclerosis				
subjects affected / exposed	2 / 1094 (0.18%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				
subjects affected / exposed	2 / 1094 (0.18%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Trigeminal neuralgia				

subjects affected / exposed	2 / 1094 (0.18%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Altered state of consciousness			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Amnesia			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebral cyst			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular insufficiency			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Convulsion			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Encephalopathy			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Epilepsy			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Facial neuralgia			

subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypoxic-ischaemic encephalopathy				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Migraine				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sciatica				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Coombs negative haemolytic anaemia				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Immune thrombocytopenic purpura				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Splenomegaly				

subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Eye swelling			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Glaucoma			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Retinal tear			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vision blurred			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Haemorrhoids			
subjects affected / exposed	3 / 1094 (0.27%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Abdominal adhesions			
subjects affected / exposed	2 / 1094 (0.18%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	2 / 1094 (0.18%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Anal fissure			

subjects affected / exposed	2 / 1094 (0.18%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	2 / 1094 (0.18%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			
subjects affected / exposed	2 / 1094 (0.18%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Abdominal hernia			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain upper			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colitis ischaemic			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diverticular perforation			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Duodenitis			

subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Faecaloma				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Flatulence				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Functional gastrointestinal disorder				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastric ulcer haemorrhage				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Inguinal hernia				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Irritable bowel syndrome				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Large intestine polyp				

subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Proctalgia			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rectal prolapse			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Small intestinal obstruction			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Umbilical hernia			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oesophageal ulcer			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	5 / 1094 (0.46%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Cholecystitis			
subjects affected / exposed	2 / 1094 (0.18%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Bile duct stone			

subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholecystitis acute			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholecystitis chronic			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Melanocytic hyperplasia			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin disorder			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	3 / 1094 (0.27%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Haematuria			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neurogenic bladder			

subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure acute			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary retention			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Goitre			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperthyroidism			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	5 / 1094 (0.46%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			
subjects affected / exposed	3 / 1094 (0.27%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Arthralgia			
subjects affected / exposed	2 / 1094 (0.18%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		

Spinal column stenosis			
subjects affected / exposed	2 / 1094 (0.18%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Arthritis			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bursitis			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Joint instability			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Joint stiffness			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Muscular weakness			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal disorder			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteonecrosis			

subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rotator cuff syndrome				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal osteoarthritis				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tenosynovitis				
subjects affected / exposed	1 / 1094 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Progressive multifocal leukoencephalopathy				
subjects affected / exposed	18 / 1094 (1.65%)			
occurrences causally related to treatment / all	18 / 18			
deaths causally related to treatment / all	1 / 1			
Urinary tract infection				
subjects affected / exposed	13 / 1094 (1.19%)			
occurrences causally related to treatment / all	1 / 18			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	4 / 1094 (0.37%)			
occurrences causally related to treatment / all	0 / 7			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	3 / 1094 (0.27%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Bronchitis viral				

subjects affected / exposed	2 / 1094 (0.18%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cystitis			
subjects affected / exposed	2 / 1094 (0.18%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	2 / 1094 (0.18%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Staphylococcal infection			
subjects affected / exposed	2 / 1094 (0.18%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Appendicitis			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atypical pneumonia			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchopneumonia			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Catheter site infection			

subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device related sepsis			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Epididymitis			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis viral			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatitis A			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Herpes zoster			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection viral			

subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung infection			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Meningitis viral			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nasopharyngitis			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oral candidiasis			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pelvic inflammatory disease			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peritonitis			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pharyngitis			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia pneumococcal			

subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia streptococcal			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sinusitis			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tooth abscess			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wound infection			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 1094 (0.09%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Natalizumab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	752 / 1094 (68.74%)		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	61 / 1094 (5.58%)		
occurrences (all)	83		
Nervous system disorders			
Multiple sclerosis relapse			
subjects affected / exposed	164 / 1094 (14.99%)		
occurrences (all)	193		
Headache			
subjects affected / exposed	157 / 1094 (14.35%)		
occurrences (all)	303		
Dizziness			
subjects affected / exposed	62 / 1094 (5.67%)		
occurrences (all)	74		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	102 / 1094 (9.32%)		
occurrences (all)	112		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	80 / 1094 (7.31%)		
occurrences (all)	118		
Psychiatric disorders			
Depression			
subjects affected / exposed	72 / 1094 (6.58%)		
occurrences (all)	81		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	113 / 1094 (10.33%)		
occurrences (all)	149		
Arthralgia			

subjects affected / exposed	86 / 1094 (7.86%)		
occurrences (all)	114		
Pain in extremity			
subjects affected / exposed	62 / 1094 (5.67%)		
occurrences (all)	86		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	256 / 1094 (23.40%)		
occurrences (all)	618		
Upper respiratory tract infection			
subjects affected / exposed	192 / 1094 (17.55%)		
occurrences (all)	394		
Urinary tract infection			
subjects affected / exposed	162 / 1094 (14.81%)		
occurrences (all)	381		
Influenza			
subjects affected / exposed	122 / 1094 (11.15%)		
occurrences (all)	159		
Sinusitis			
subjects affected / exposed	82 / 1094 (7.50%)		
occurrences (all)	110		
Bronchitis			
subjects affected / exposed	67 / 1094 (6.12%)		
occurrences (all)	96		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 March 2006	• Changes to exclusion criteria • Addition of pregnancy precautions • Additional follow-up visits added
29 January 2007	• Long-term Follow-Up, extension of the study
23 March 2007	• Addition of Canadian sites • Antibody testing for allergic reaction
12 March 2010	• Addition of blood and urine samples for John Cunningham Virus (JCV) research • Addition of annual magnetic resonance imaging (MRI) • Permission for pregnant patients to return to study
10 January 2011	• Extension of the study to 480 weeks (This amendment was not implemented; the changes detailed in this version were included in Protocol Version 7 [04 March 2011].)
04 March 2011	• Extended the study by 216 weeks to give a total study duration of 480 weeks • Addition of anti-JCV antibody testing every 12 weeks if JCV antibody is positive • Progressive multifocal leukoencephalopathy samples and genetic samples • Axial fluid-attenuated inversion recovery MRI
14 February 2013	• Removed requirement for anti-JCV antibody positive patients to provide samples every 12 weeks. All patients to provide samples every 24 weeks • Removed MRI substudy • Added exploratory analysis of long-term MRI changes • Specified 12-week Telephone Follow-Up only required for subjects discontinuing treatment with natalizumab

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Sponsor decided to terminate the study prior to all subjects reaching Week 480 as the primary objective was deemed to have been met and only approximately 45% of the original STRATA population remained in the study at the time of study termination.

Notes: