Clinical trial results:
A Dose-Blind, Multicenter, Extension Study to Determine the Long-Term Safety and Efficacy of Two Doses of BG00012 Monotherapy in Subjects with Relapsing-Remitting Multiple Sclerosis

Summary

EudraCT number	2008-004753-14
Trial protocol	BE CZ SK DE IE LV ES FR EE GR AT NL BG IT GB
Global end of trial date	08 November 2019

Results information

Result version number	v2 (current)
This version publication date	22 February 2021
First version publication date	06 November 2020
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	109MS303

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00835770
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Biogen
Sponsor organisation address	250 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	08 November 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 November 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to evaluate the long-term safety profile of BG00012.

Protection of trial subjects:

Written informed consent was obtained from each subject or subject's legally authorized representative (e.g., parent or legal guardian), as applicable, prior to evaluations performed for eligibility. Subjects or the subject's legally authorized representative were given adequate time to review the information in the informed consent/assent and were allowed to ask, and have answered, questions concerning all portions of the conduct of the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 February 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	Poland: 308
Country: Number of subjects enrolled	United States: 267
Country: Number of subjects enrolled	India: 162
Country: Number of subjects enrolled	Germany: 160
Country: Number of subjects enrolled	Ukraine: 104
Country: Number of subjects enrolled	Czechia: 98
Country: Number of subjects enrolled	Serbia: 86
Country: Number of subjects enrolled	France: 69
Country: Number of subjects enrolled	Belgium: 41
Country: Number of subjects enrolled	Canada: 40
Country: Number of subjects enrolled	Mexico: 38
Country: Number of subjects enrolled	Bulgaria: 33
Country: Number of subjects enrolled	Australia: 26
Country: Number of subjects enrolled	Spain: 26
Country: Number of subjects enrolled	Moldova, Republic of: 24
Country: Number of subjects enrolled	Romania: 23
Country: Number of subjects enrolled	United Kingdom: 22
Country: Number of subjects enrolled	Belarus: 20
Country: Number of subjects enrolled	Estonia: 19

Country: Number of subjects enrolled	Greece: 19
Country: Number of subjects enrolled	North Macedonia: 19
Country: Number of subjects enrolled	Slovakia: 18
Country: Number of subjects enrolled	Bosnia and Herzegovina: 15
Country: Number of subjects enrolled	Croatia: 14
Country: Number of subjects enrolled	New Zealand: 14
Country: Number of subjects enrolled	Switzerland: 14
Country: Number of subjects enrolled	Latvia: 11
Country: Number of subjects enrolled	Austria: 10
Country: Number of subjects enrolled	Israel: 9
Country: Number of subjects enrolled	South Africa: 8
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Guatemala: 5
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Ireland: 3
Country: Number of subjects enrolled	Puerto Rico: 3
Worldwide total number of subjects	1738
EEA total number of subjects	862

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)	1738
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled at 298 investigative sites from 03 February 2009 to 08 November 2019.

Pre-assignment

Screening details:

The study included subjects who completed studies 2006-003696-12 and 2006-003697-10. A total of 1736 subjects were treated in the open-label phase extension study 2008-004753-14, out of which 759 completed the study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	BG00012 240 mg BID

Arm description:

Subjects received BG00012 240 milligrams (mg) (120 mg each) 2 capsules orally, twice a day (BID) and 2 matching placebo capsules once a day (QD) up to 8 years.

Arm type	Experimental
Investigational medicinal product name	BG00012
Investigational medicinal product code	
Other name	Dimethly fumarate
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received BG00012 240 mg (120 mg each) 2 capsules orally, BID up to 8 years.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received 2 matching placebo to BG00012 capsules QD up to 8 years.

Arm title	BG00012 240 mg TID

Arm description:

Subjects received BG00012 240 mg (120 mg each) 2 capsules orally, three times a day (TID) up to 8 years.

Arm type	Experimental
Investigational medicinal product name	BG00012
Investigational medicinal product code	
Other name	Dimethly fumarate
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received BG00012 240 mg (120 mg each) 2 capsules orally, TID up to 8 years.

Number of subjects in period 1[1]	BG00012 240 mg BID	BG00012 240 mg TID
Started	868	868
Completed	384	375
Not completed	484	493
Subject Non-Compliance	11	9
MS progression	14	9
Adverse Event	113	124
Death	4	6
Not specified	115	104
Unknown	2	1
Investigator decision	42	42
Lost to follow-up	22	19
Consent withdrawn	144	156
MS relapse	17	23

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The number of subjects reported in the baseline period is for intent to treat population (868 subjects in BG00012 240 mg BID, 868 subjects in BG00012 240 mg TID).

Baseline characteristics

Reporting groups	
Reporting group title	BG00012 240 mg BID
Reporting group description:	
Subjects received BG00012 240 milligrams (mg) (120 mg each) 2 capsules orally, twice a day (BID) and 2 matching placebo capsules once a day (QD) up to 8 years.	
Reporting group title	BG00012 240 mg TID
Reporting group description:	
Subjects received BG00012 240 mg (120 mg each) 2 capsules orally, three times a day (TID) up to 8 years.	

Reporting group values	BG00012 240 mg BID	BG00012 240 mg TID	Total
Number of subjects	868	868	1736
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	39.6	40.1	
standard deviation	± 8.93	± 9.23	-
Sex: Female, Male Units: subjects			
Female	616	596	1212
Male	252	272	524
Race/Ethnicity, Customized Units: Subjects			
White	285	309	594
Black or African American	10	16	26
Asian	82	80	162
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Other	32	24	56
Not Reported Due To Confidentiality Regulations	459	439	898

End points

End points reporting groups

Reporting group title	BG00012 240 mg BID
Reporting group description:	
Subjects received BG00012 240 milligrams (mg) (120 mg each) 2 capsules orally, twice a day (BID) and 2 matching placebo capsules once a day (QD) up to 8 years.	
Reporting group title	BG00012 240 mg TID
Reporting group description:	
Subjects received BG00012 240 mg (120 mg each) 2 capsules orally, three times a day (TID) up to 8 years.	
Subject analysis set title	BG00012 240 mg BID (Prior BG00012 240 mg BID)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subjects received BG00012 240 mg, 2 capsules (120 mg each) orally, BID and 2 matching placebo capsules QD for up to 8 years. Subjects who had received BG00012 240 mg BID in the previous studies were included in this arm group.	
Subject analysis set title	BG00012 240 mg TID (Prior BG00012 240 mg TID)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subjects received BG00012 240 mg, 2 capsules (120 mg each) orally, TID for up to 8 years. Subjects who had received BG00012 240 mg TID in the previous studies were included in this arm group.	
Subject analysis set title	BG00012 240 mg BID (Prior BG00012 Matched Placebo)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subjects received BG00012 240 mg, 2 capsules (120 mg each) orally, BID and 2 matching placebo capsules QD for up to 8 years. Subjects who had received placebo matched to BG00012 in the previous studies were included in this arm group.	
Subject analysis set title	BG00012 240 mg TID (Prior BG00012 Matched Placebo)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subjects received BG00012 240 mg, 2 capsules (120 mg each) orally, TID for up to 8 years. Subjects who had received placebo matched to BG00012 in the previous studies were included in this arm group.	
Subject analysis set title	BG00012 240 mg BID (Prior Glatiramer Acetate [GA])
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subjects received BG00012 240 mg, 2 capsules (120 mg each) orally, BID and 2 matching placebo capsules QD for up to 8 years. Subjects who had received Glatiramer Acetate (GA) in the previous studies were included in this arm group.	
Subject analysis set title	BG00012 240 mg TID (Prior Glatiramer Acetate [GA])
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subjects received BG00012 240 mg, 2 capsules (120 mg each) orally, TID for up to 8 years. Subjects who had received GA in the previous studies were included in this arm group.	
Subject analysis set title	BG00012 240 mg BID (Prior BG00012 240 mg BID)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects received BG00012 240 mg, 2 capsules (120 mg each) orally, BID and 2 matching placebo capsules QD for up to 8 years. Subjects who had received BG00012 240 mg BID in the previous studies were included in this arm group.	
Subject analysis set title	BG00012 240 mg TID (Prior BG00012 240 mg TID)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects received BG00012 240 mg, 2 capsules (120 mg each) orally, TID for up to 8 years. Subjects who had received BG00012 240 mg TID in the previous studies were included in this arm group.	

Subject analysis set title	BG00012 240 mg BID (Prior BG00012 Matched Placebo)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received BG00012 240 mg, 2 capsules (120 mg each) orally, BID and 2 matching placebo capsules QD for up to 8 years. Subjects who had received placebo matched to BG00012 in the previous studies were included in this arm group.

Subject analysis set title	BG00012 240 mg TID (Prior BG00012 Matched Placebo)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received BG00012 240 mg, 2 capsules (120 mg each) orally, TID for up to 8 years. Subjects who had received placebo matched to BG00012 in the previous studies were included in this arm group.

Subject analysis set title	BG00012 240 mg BID (Prior Glatiramer Acetate [GA])
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received BG00012 240 mg, 2 capsules (120 mg each) orally, BID and 2 matching placebo capsules QD for up to 8 years. Subjects who had received Glatiramer Acetate (GA) in the previous studies were included in this arm group.

Subject analysis set title	BG00012 240 mg TID (Prior Glatiramer Acetate [GA])
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received BG00012 240 mg, 2 capsules (120 mg each) orally, TID for up to 8 years. Subjects who had received GA in the previous studies were included in this arm group.

Primary: Number of Subjects with Treatment-Emergent Adverse Events (AEs)

End point title	Number of Subjects with Treatment-Emergent Adverse Events (AEs)[1]

End point description:

An adverse event (AE) is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. Safety population included all subjects who had any post-baseline safety follow-up in study 2008-004753-14, defined as any treatment emergent AE in study 2008-004753-14 or any post-baseline laboratory, vital signs, or physical exam assessment in study 2008-004753-14, and received at least one dose of study treatment in study 2008-004753-14.

End point type	Primary

End point timeframe:

Day 1 up to Week 561

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 analysis was planned to be performed.

End point values	BG00012 240 mg BID	BG00012 240 mg TID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	868	868		
Units: subjects	824	814		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Had Relapses

End point title	Percentage of Subjects Who Had Relapses

End point description:

Relapses were defined as new or recurrent neurologic symptoms not associated with fever or infection, lasting at least 24 hours. ITT population included subjects who had entered study 2008-004753-14 and received at least one dose of study treatment. Data for this endpoint was summarised as per treatment received in previous studies (2006-003696-12 and 2006-003697-10).

End point type	Secondary

End point timeframe:

Day 1 up to Week 384

End point values	BG00012 240 mg BID (Prior BG00012 240 mg BID)	BG00012 240 mg TID (Prior BG00012 240 mg TID)	BG00012 240 mg BID (Prior BG00012 Matched Placebo)	BG00012 240 mg TID (Prior BG00012 Matched Placebo)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	501	502	249	248
Units: percentage of subjects	40	41	34	36

End point values	BG00012 240 mg BID (Prior Glatiramer Acetate [GA])	BG00012 240 mg TID (Prior Glatiramer Acetate [GA])		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	118	118		
Units: percentage of subjects	31	31		

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Relapse Rate (ARR)

End point title	Annualized Relapse Rate (ARR)

End point description:

The annualized relapse rate is calculated as the total number of relapses occurred during the period for all subjects, divided by the total number of subject-years followed in the period. ITT population included subjects who had entered study 2008-004753-14 and received at least one dose of study treatment. Data for this endpoint was summarised as per treatment received in previous studies (2006-003696-12 and 2006-003697-10).

End point type	Secondary

End point timeframe:

Day 1 up to Week 384

End point values	BG00012 240 mg BID (Prior BG00012 240 mg BID)	BG00012 240 mg TID (Prior BG00012 240 mg TID)	BG00012 240 mg BID (Prior BG00012 Matched Placebo)	BG00012 240 mg TID (Prior BG00012 Matched Placebo)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	501	502	249	248
Units: relapses per subject-years				
number (not applicable)	0.159	0.179	0.200	0.199

End point values	BG00012 240 mg BID (Prior Glatiramer Acetate [GA])	BG00012 240 mg TID (Prior Glatiramer Acetate [GA])		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	118	118		
Units: relapses per subject-years				
number (not applicable)	0.184	0.212		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Expanded Disability Status Scale (EDSS) at Week 384

End point title	Change from Baseline in the Expanded Disability Status Scale (EDSS) at Week 384

End point description:

The EDSS scale ranges from 0 (Normal neurological exam, no disability) to 10 (Death) in 0.5 unit increments that represent higher levels of disability. Scoring is based on an examination by a neurologist. Progression of disability was defined as at least a 1.0 point increase on the EDSS from a baseline EDSS >=1.0 that was sustained for at least 24 weeks, or a 1.5 point increase on the EDSS from a baseline EDSS =0 that was sustained for at least 24 weeks. ITT population included subjects who had entered study 2008-004753-14 and received at least one dose of study treatment. Here, 'n' signifies number of subjects analysed at specific timepoint. Data for this endpoint was summarised as per treatment received in previous studies (2006-003696-12 and 2006-003697-10).

End point type	Secondary

End point timeframe:

Baseline, Week 384

End point values	BG00012 240 mg BID (Prior BG00012 240 mg BID)	BG00012 240 mg TID (Prior BG00012 240 mg TID)	BG00012 240 mg BID (Prior BG00012 Matched Placebo)	BG00012 240 mg TID (Prior BG00012 Matched Placebo)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	501	502	249	248
Units: score on a scale				
arithmetic mean (standard deviation)				

Baseline (n =499, 502, 249, 248, 118, 118)	2.44 (± 1.251)	2.43 (± 1.144)	2.50 (± 1.135)	2.54 (± 1.218)
Change at Week 384 (n =226, 219, 90, 98, 42, 50)	0.28 (± 1.160)	0.26 (± 1.213)	0.37 (± 1.328)	0.53 (± 1.278)

End point values	BG00012 240 mg BID (Prior Glatiramer Acetate [GA])	BG00012 240 mg TID (Prior Glatiramer Acetate [GA])		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	118	118		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline (n =499, 502, 249, 248, 118, 118)	2.57 (± 1.249)	2.68 (± 1.231)		
Change at Week 384 (n =226, 219, 90, 98, 42, 50)	0.39 (± 1.217)	0.49 (± 1.319)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Gadolinium (Gd)-Enhancing Lesions as Measured by Magnetic Resonance Imaging (MRI)

End point title	Number of Gadolinium (Gd)-Enhancing Lesions as Measured by Magnetic Resonance Imaging (MRI)

End point description:

The Gd-enhancing lesions were evaluated using MRI technique. MRI cohort included subjects in the study 2008-004753-14 ITT population who had consented to participate in the MRI sub-study and have any MRI data in Studies 2006-003696-12,2006-003697-10or 2008-004753-14. Here, 'n' signifies number of subjects analysed at specific timepoint. Data for this endpoint was summarised as per the treatment received in previous studies (2006-003696-12 and 2006-003697-10).

End point type	Secondary

End point timeframe:

Baseline up to Week 288

End point values	BG00012 240 mg BID (Prior BG00012 240 mg BID)	BG00012 240 mg TID (Prior BG00012 240 mg TID)	BG00012 240 mg BID (Prior BG00012 Matched Placebo)	BG00012 240 mg TID (Prior BG00012 Matched Placebo)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	213	222	105	103
Units: lesions				
arithmetic mean (standard deviation)				
Week 48 (n =191, 195, 83, 78, 41, 48)	0.4 (± 1.87)	0.4 (± 1.29)	0.2 (± 0.66)	0.3 (± 1.14)
Week 96 (n =183, 186, 77, 75, 39, 46)	0.4 (± 1.77)	0.4 (± 1.28)	0.1 (± 0.38)	0.2 (± 0.82)
Week 144 (n =156, 159, 66, 60, 32, 41)	0.3 (± 1.66)	0.4 (± 1.30)	0.2 (± 0.44)	0.1 (± 0.29)

Week 192 (n =144, 149, 59, 55, 33, 38)	0.4 (± 2.02)	0.5 (± 1.85)	0.5 (± 1.72)	0.3 (± 0.96)
Week 240 (n =135, 134, 55, 53, 29, 34)	0.5 (± 3.14)	0.5 (± 2.29)	0.2 (± 0.50)	0.2 (± 0.51)
Week 288 (n =89, 97, 30, 31, 6, 16)	0.2 (± 0.74)	0.5 (± 1.81)	0.1 (± 0.40)	0.7 (± 2.76)

End point values	BG00012 240 mg BID (Prior Glatiramer Acetate [GA])	BG00012 240 mg TID (Prior Glatiramer Acetate [GA])		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	49	60		
Units: lesions				
arithmetic mean (standard deviation)				
Week 48 (n =191, 195, 83, 78, 41, 48)	0.5 (± 1.19)	0.4 (± 1.14)		
Week 96 (n =183, 186, 77, 75, 39, 46)	0.6 (± 1.33)	0.3 (± 0.73)		
Week 144 (n =156, 159, 66, 60, 32, 41)	0.5 (± 2.48)	0.3 (± 1.59)		
Week 192 (n =144, 149, 59, 55, 33, 38)	0.2 (± 0.60)	0.6 (± 2.01)		
Week 240 (n =135, 134, 55, 53, 29, 34)	0.2 (± 0.58)	0.3 (± 0.75)		
Week 288 (n =89, 97, 30, 31, 6, 16)	0.0 (± 0.00)	0.3 (± 0.77)		

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of Gd-Enhancing Lesions as Measured by Magnetic Resonance Imaging (MRI)

End point title	Volume of Gd-Enhancing Lesions as Measured by Magnetic Resonance Imaging (MRI)

End point description:

The Gd-enhancing lesions were evaluated using MRI technique. MRI cohort included subjects in the study 2008-004753-14 ITT population who had consented to participate in the MRI sub-study and have any MRI data in Studies 2006-003696-12,2006-003697-10or 2008-004753-14. Here, 'n' signifies number of subjects analysed at specific timepoint. Data for this endpoint was summarised as per the treatment received in previous studies (2006-003696-12 and 2006-003697-10).

End point type	Secondary

End point timeframe:

Baseline up to Week 288

End point values	BG00012 240 mg BID (Prior BG00012 240 mg BID)	BG00012 240 mg TID (Prior BG00012 240 mg TID)	BG00012 240 mg BID (Prior BG00012 Matched Placebo)	BG00012 240 mg TID (Prior BG00012 Matched Placebo)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	213	222	105	103
Units: millimetre cube (mm^3)				
arithmetic mean (standard deviation)				
Baseline (n =209, 220, 104, 99, 47, 60)	31.7 (± 179.28)	48.6 (± 205.43)	96.0 (± 260.79)	142.5 (± 459.76)
Week 48 (n =190, 197, 83, 77, 40, 48)	59.6 (± 526.51)	70.0 (± 366.63)	18.8 (± 91.47)	25.3 (± 108.19)
Week 96 (n =182, 185, 77, 73, 38, 46)	49.1 (± 245.14)	56.1 (± 271.29)	27.7 (± 204.80)	13.3 (± 67.01)
Week 144 (n =155, 160, 66, 59, 31, 41)	44.1 (± 291.14)	47.0 (± 169.68)	18.8 (± 66.15)	3.8 (± 25.03)
Week 192 (n =143, 148, 59, 54, 32, 38)	39.1 (± 217.89)	54.5 (± 251.31)	45.8 (± 156.88)	19.9 (± 79.19)
Week 240 (n =134, 133, 55, 52, 28, 34)	96.8 (± 650.06)	69.3 (± 374.67)	21.7 (± 77.87)	14.1 (± 45.22)
Week 288 (n =89, 97, 30, 31, 6, 16)	18.2 (± 93.28)	53.1 (± 250.87)	7.9 (± 30.09)	230.2 (± 1092.11)

End point values	BG00012 240 mg BID (Prior Glatiramer Acetate [GA])	BG00012 240 mg TID (Prior Glatiramer Acetate [GA])		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	49	60		
Units: millimetre cube (mm^3)				
arithmetic mean (standard deviation)				
Baseline (n =209, 220, 104, 99, 47, 60)	37.1 (± 138.82)	41.7 (± 116.55)		
Week 48 (n =190, 197, 83, 77, 40, 48)	42.5 (± 123.67)	42.7 (± 148.11)		
Week 96 (n =182, 185, 77, 73, 38, 46)	64.3 (± 183.16)	22.3 (± 60.83)		
Week 144 (n =155, 160, 66, 59, 31, 41)	42.6 (± 142.55)	92.9 (± 397.69)		
Week 192 (n =143, 148, 59, 54, 32, 38)	12.0 (± 40.56)	55.1 (± 169.16)		
Week 240 (n =134, 133, 55, 52, 28, 34)	17.5 (± 46.19)	17.1 (± 48.41)		
Week 288 (n =89, 97, 30, 31, 6, 16)	0.0 (± 0.00)	34.1 (± 102.87)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of New or Newly Enlarging T2 Lesions as Measured by Magnetic Resonance Imaging (MRI)

End point title	Number of New or Newly Enlarging T2 Lesions as Measured by Magnetic Resonance Imaging (MRI)

End point description:

The T2 lesions were evaluated using MRI technique. MRI cohort included subjects in the study 2008-004753-14 ITT population who had consented to participate in the MRI sub-study and have any MRI data in Studies 2006-003696-12,2006-003697-10or 2008-004753-14. Here, 'n' signifies number of subjects analysed at specific timepoint. Data for this endpoint was summarised as per the treatment received in previous studies (2006-003696-12 and 2006-003697-10).

End point type	Secondary

End point timeframe:

Baseline up to Week 288

End point values	BG00012 240 mg BID (Prior BG00012 240 mg BID)	BG00012 240 mg TID (Prior BG00012 240 mg TID)	BG00012 240 mg BID (Prior BG00012 Matched Placebo)	BG00012 240 mg TID (Prior BG00012 Matched Placebo)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	213	222	105	103
Units: lesions				
arithmetic mean (standard deviation)				
Week 48 (n =198, 201, 84, 81, 42, 50)	1.6 (± 4.07)	2.2 (± 6.15)	2.7 (± 4.96)	2.4 (± 5.45)
Week 96 (n =191, 192, 78, 77, 40, 47)	3.4 (± 8.35)	4.1 (± 10.01)	3.8 (± 7.24)	2.9 (± 6.78)
Week 144 (n =163, 168, 67, 63, 35, 44)	4.2 (± 9.81)	5.2 (± 10.01)	4.0 (± 7.27)	4.3 (± 10.12)
Week 192 (n =151, 155, 61, 56, 33, 40)	5.8 (± 14.04)	7.5 (± 15.14)	5.6 (± 10.09)	5.6 (± 14.19)
Week 240 (n =139, 142, 55, 55, 30, 37)	7.4 (± 17.09)	9.5 (± 20.33)	8.2 (± 14.87)	7.7 (± 17.89)
Week 288 (n =123, 123, 45, 49, 26, 32)	8.2 (± 18.53)	12.4 (± 28.23)	7.5 (± 13.89)	10.4 (± 22.05)

End point values	BG00012 240 mg BID (Prior Glatiramer Acetate [GA])	BG00012 240 mg TID (Prior Glatiramer Acetate [GA])		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	49	60		
Units: lesions				
arithmetic mean (standard deviation)				
Week 48 (n =198, 201, 84, 81, 42, 50)	3.4 (± 6.57)	2.1 (± 3.83)		
Week 96 (n =191, 192, 78, 77, 40, 47)	4.9 (± 8.51)	3.4 (± 5.13)		
Week 144 (n =163, 168, 67, 63, 35, 44)	5.7 (± 9.45)	5.2 (± 9.68)		
Week 192 (n =151, 155, 61, 56, 33, 40)	5.5 (± 9.94)	5.6 (± 13.35)		
Week 240 (n =139, 142, 55, 55, 30, 37)	6.8 (± 11.74)	7.5 (± 16.76)		
Week 288 (n =123, 123, 45, 49, 26, 32)	8.9 (± 15.04)	6.0 (± 8.90)		

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of New or Newly Enlarging T2 Lesions as Measured by Magnetic Resonance Imaging (MRI)

End point title	Volume of New or Newly Enlarging T2 Lesions as Measured by Magnetic Resonance Imaging (MRI)

End point description:

The T2 lesions were evaluated using MRI technique.MRI cohort included subjects in the study 2008-004753-14 ITT population who had consented to participate in the MRI sub-study and have any MRI data in Studies 2006-003696-12,2006-003697-10or 2008-004753-14. Here, 'n' signifies number of subjects analysed at specific timepoint. Data for this endpoint was summarised as per the treatment received in previous studies (2006-003696-12 and 2006-003697-10).

End point type	Secondary

End point timeframe:

Baseline up to Week 288

End point values	BG00012 240 mg BID (Prior BG00012 240 mg BID)	BG00012 240 mg TID (Prior BG00012 240 mg TID)	BG00012 240 mg BID (Prior BG00012 Matched Placebo)	BG00012 240 mg TID (Prior BG00012 Matched Placebo)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	213	222	105	103
Units: mm^3				
arithmetic mean (standard deviation)				
Baseline (n =209, 220, 104, 99, 47, 60)	10231.9 (± 11214.17)	10408.3 (± 12166.80)	8883.7 (± 8570.10)	10806.3 (± 12060.05)
Week 48 (n =194, 199, 84, 78, 40, 50)	9951.9 (± 10750.15)	9849.6 (± 10986.36)	8992.1 (± 7952.13)	10114.5 (± 10121.61)
Week 96 (n =187, 190, 78, 74, 38, 47)	10331.3 (± 11359.81)	10434.0 (± 12201.38)	8645.2 (± 7787.60)	9985.7 (± 10715.73)
Week 144 (n =162, 167, 67, 61, 34, 44)	9930.1 (± 10686.26)	10280.7 (± 11324.58)	8829.4 (± 7482.93)	9792.3 (± 9842.28)
Week 192 (n =149, 154, 61, 55, 32, 40)	9837.7 (± 10845.04)	10760.0 (± 11987.16)	9077.6 (± 7794.52)	10576.3 (± 12029.26)
Week 240 (n =138, 141, 55, 54, 29, 37)	10611.2 (± 11633.95)	11087.5 (± 12464.90)	9711.1 (± 8709.46)	10591.4 (± 11613.26)
Week 288 (n =121, 122, 45, 49, 26, 32)	9611.8 (± 9447.18)	9800.8 (± 11279.84)	8819.8 (± 8866.90)	10537.6 (± 10684.47)

End point values	BG00012 240 mg BID (Prior Glatiramer Acetate [GA])	BG00012 240 mg TID (Prior Glatiramer Acetate [GA])		

Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	49	60		
Units: mm^3				
arithmetic mean (standard deviation)				
Baseline (n =209, 220, 104, 99, 47, 60)	12628.9 (± 11258.69)	13044.4 (± 14608.50)		
Week 48 (n =194, 199, 84, 78, 40, 50)	11160.7 (± 9565.55)	12979.0 (± 14415.86)		
Week 96 (n =187, 190, 78, 74, 38, 47)	11318.1 (± 9873.73)	13974.1 (± 15432.10)		
Week 144 (n =162, 167, 67, 61, 34, 44)	10188.5 (± 8064.09)	12949.7 (± 14036.15)		
Week 192 (n =149, 154, 61, 55, 32, 40)	10421.9 (± 8773.41)	11671.5 (± 13124.47)		
Week 240 (n =138, 141, 55, 54, 29, 37)	11009.9 (± 9551.94)	12254.4 (± 13732.10)		
Week 288 (n =121, 122, 45, 49, 26, 32)	11586.3 (± 9728.19)	10404.8 (± 12245.75)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of T1 Hypointense Lesions as Measured by Magnetic Resonance Imaging (MRI)

End point title	Number of T1 Hypointense Lesions as Measured by Magnetic Resonance Imaging (MRI)

End point description:

The T1 hypointense lesions were evaluated using MRI technique. MRI cohort included subjects in the study 2008-004753-14 ITT population who had consented to participate in the MRI sub-study and have any MRI data in Studies 2006-003696-12,2006-003697-10or 2008-004753-14. Here, 'n' signifies number of subjects analysed at specific timepoint. Data for this endpoint was summarised as per the treatment received in previous studies (2006-003696-12 and 2006-003697-10).

End point type	Secondary

End point timeframe:

Baseline up to Week 288

End point values	BG00012 240 mg BID (Prior BG00012 240 mg BID)	BG00012 240 mg TID (Prior BG00012 240 mg TID)	BG00012 240 mg BID (Prior BG00012 Matched Placebo)	BG00012 240 mg TID (Prior BG00012 Matched Placebo)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	213	222	105	103
Units: lesions				
arithmetic mean (standard deviation)				
Week 48 (n =183, 184, 79, 76, 41, 48)	0.8 (± 2.13)	1.0 (± 2.37)	1.8 (± 3.81)	1.7 (± 3.71)
Week 96 (n =171, 178, 75, 72, 39, 45)	1.7 (± 3.63)	1.9 (± 3.91)	1.8 (± 3.33)	2.1 (± 5.00)
Week 144 (n =148, 155, 63, 53, 32, 41)	2.0 (± 4.61)	2.8 (± 5.19)	2.0 (± 3.69)	2.6 (± 7.02)
Week 192 (n =141, 145, 58, 53, 33, 38)	2.9 (± 7.03)	3.4 (± 6.79)	2.9 (± 5.12)	3.8 (± 10.71)

Week 240 (n =134, 136, 55, 53, 29, 34)	3.4 (± 8.25)	4.8 (± 9.39)	4.0 (± 7.52)	4.9 (± 13.30)
Week 288 (n =88, 94, 30, 32, 6, 16)	2.7 (± 5.72)	5.9 (± 12.02)	4.5 (± 7.38)	3.6 (± 4.51)

End point values	BG00012 240 mg BID (Prior Glatiramer Acetate [GA])	BG00012 240 mg TID (Prior Glatiramer Acetate [GA])		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	49	60		
Units: lesions				
arithmetic mean (standard deviation)				
Week 48 (n =183, 184, 79, 76, 41, 48)	2.0 (± 4.22)	1.3 (± 2.64)		
Week 96 (n =171, 178, 75, 72, 39, 45)	3.0 (± 5.85)	1.9 (± 3.44)		
Week 144 (n =148, 155, 63, 53, 32, 41)	3.1 (± 6.20)	2.9 (± 5.19)		
Week 192 (n =141, 145, 58, 53, 33, 38)	3.3 (± 6.74)	3.0 (± 7.14)		
Week 240 (n =134, 136, 55, 53, 29, 34)	4.0 (± 8.06)	4.2 (± 10.20)		
Week 288 (n =88, 94, 30, 32, 6, 16)	1.0 (± 1.10)	5.6 (± 6.81)		

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of T1 Hypointense Lesions as Measured by Magnetic Resonance Imaging (MRI)

End point title	Volume of T1 Hypointense Lesions as Measured by Magnetic Resonance Imaging (MRI)

End point description:

The T1 hypointense lesions were evaluated using MRI technique. MRI cohort included subjects in the study 2008-004753-14 ITT population who had consented to participate in the MRI sub-study and have any MRI data in Studies 2006-003696-12,2006-003697-10or 2008-004753-14. Here, 'n' signifies number of subjects analysed at specific timepoint. Data for this endpoint was summarised as per the treatment received in previous studies (2006-003696-12 and 2006-003697-10).

End point type	Secondary

End point timeframe:

Baseline up to Week 288

End point values	BG00012 240 mg BID (Prior BG00012 240 mg BID)	BG00012 240 mg TID (Prior BG00012 240 mg TID)	BG00012 240 mg BID (Prior BG00012 Matched Placebo)	BG00012 240 mg TID (Prior BG00012 Matched Placebo)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	213	222	105	103
Units: mm^3				
arithmetic mean (standard deviation)				

Baseline (n =209, 220, 104, 99, 47, 60)	3640.1 (± 5598.31)	3447.3 (± 4900.96)	2754.2 (± 3552.30)	3623.1 (± 5549.13)
Week 48 (n =190, 197, 83, 77, 40, 48)	3829.5 (± 5824.26)	3715.5 (± 5112.21)	2891.9 (± 3034.00)	3936.0 (± 5271.89)
Week 96 (n =183, 186, 77, 73, 38, 46)	3841.2 (± 5682.74)	3853.7 (± 5428.66)	2921.0 (± 3327.93)	3849.4 (± 5167.13)
Week 144 (n =157, 164, 67, 58, 33, 42)	3767.4 (± 4969.23)	4074.0 (± 5413.85)	3145.6 (± 3366.27)	4006.9 (± 5062.08)
Week 192 (n =145, 149, 60, 54, 32, 38)	3834.9 (± 4942.19)	4177.4 (± 5301.68)	3385.4 (± 3575.44)	4330.0 (± 5136.67)
Week 240 (n =135, 137, 55, 52, 28, 34)	4038.6 (± 5145.85)	4238.2 (± 5248.84)	3406.4 (± 3936.73)	3823.9 (± 4274.82)
Week 288 (n =113, 121, 40, 45, 20, 29)	3603.3 (± 4394.60)	3973.1 (± 5202.05)	3350.6 (± 4140.34)	4187.5 (± 4835.43)

End point values	BG00012 240 mg BID (Prior Glatiramer Acetate [GA])	BG00012 240 mg TID (Prior Glatiramer Acetate [GA])		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	49	60		
Units: mm^3				
arithmetic mean (standard deviation)				
Baseline (n =209, 220, 104, 99, 47, 60)	3204.3 (± 4221.55)	3572.6 (± 4915.24)		
Week 48 (n =190, 197, 83, 77, 40, 48)	3271.0 (± 4157.24)	3743.3 (± 5374.24)		
Week 96 (n =183, 186, 77, 73, 38, 46)	3510.4 (± 4672.80)	3949.7 (± 5018.63)		
Week 144 (n =157, 164, 67, 58, 33, 42)	3499.2 (± 4198.50)	4126.1 (± 5695.44)		
Week 192 (n =145, 149, 60, 54, 32, 38)	3592.0 (± 4069.39)	4089.3 (± 4996.13)		
Week 240 (n =135, 137, 55, 52, 28, 34)	3503.4 (± 3933.75)	4057.7 (± 5223.62)		
Week 288 (n =113, 121, 40, 45, 20, 29)	3264.9 (± 3639.91)	2959.1 (± 3918.62)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline in Brain Atrophy

End point title	Percent Change from Baseline in Brain Atrophy

End point description:

Brain atrophy was measured using magnetic resonance imaging (MRI) technique. MRI cohort included subjects in the study 2008-004753-14 ITT population who had consented to participate in the MRI sub-study and have any MRI data in Studies 2006-003696-12,2006-003697-10or 2008-004753-14. Here, 'n' signifies number of subjects analysed at specific timepoint. Data for this endpoint was summarised as per the treatment received in previous studies (2006-003696-12 and 2006-003697-10).

End point type	Secondary

End point timeframe:

Baseline up to Week 288

End point values	BG00012 240 mg BID (Prior BG00012 240 mg BID)	BG00012 240 mg TID (Prior BG00012 240 mg TID)	BG00012 240 mg BID (Prior BG00012 Matched Placebo)	BG00012 240 mg TID (Prior BG00012 Matched Placebo)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	213	222	105	103
Units: percent change				
arithmetic mean (standard deviation)				
Change at Week 48 (n =162, 162, 56, 64, 33, 42)	-1.206 (± 1.1006)	-1.263 (± 1.0848)	-1.487 (± 1.3086)	-1.320 (± 1.4021)
Change at Week 96 (n =144, 145, 50, 56, 30, 37)	-1.372 (± 1.1382)	-1.500 (± 1.0893)	-1.589 (± 1.3630)	-1.775 (± 1.7191)
Change at Week 144 (n =122, 133, 44, 49, 28, 36)	-1.708 (± 1.4109)	-1.876 (± 1.2604)	-2.139 (± 1.5884)	-2.353 (± 1.7897)
Change at Week 192 (n =114, 120, 41, 45, 29, 36)	-2.138 (± 1.6831)	-2.117 (± 1.4000)	-2.230 (± 1.7755)	-2.476 (± 1.7062)
Change at Week 240 (n =92, 95, 37, 40, 18, 26)	-2.313 (± 1.6309)	-2.253 (± 1.3721)	-2.271 (± 1.4817)	-2.593 (± 1.9043)
Change at Week 288 (n =71, 72, 25, 30, 15, 23)	-2.216 (± 1.5744)	-2.271 (± 1.2193)	-2.470 (± 1.6757)	-2.849 (± 1.9648)

End point values	BG00012 240 mg BID (Prior Glatiramer Acetate [GA])	BG00012 240 mg TID (Prior Glatiramer Acetate [GA])		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	49	60		
Units: percent change				
arithmetic mean (standard deviation)				
Change at Week 48 (n =162, 162, 56, 64, 33, 42)	-1.496 (± 1.1316)	-1.414 (± 1.1882)		
Change at Week 96 (n =144, 145, 50, 56, 30, 37)	-1.883 (± 1.2383)	-1.810 (± 1.4556)		
Change at Week 144 (n =122, 133, 44, 49, 28, 36)	-2.386 (± 1.3168)	-2.252 (± 2.2124)		
Change at Week 192 (n =114, 120, 41, 45, 29, 36)	-2.645 (± 1.2284)	-2.417 (± 2.0486)		
Change at Week 240 (n =92, 95, 37, 40, 18, 26)	-2.249 (± 1.2985)	-2.790 (± 2.2188)		
Change at Week 288 (n =71, 72, 25, 30, 15, 23)	-2.657 (± 1.7051)	-2.496 (± 1.3699)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline in Magnetization Transfer Ratio (MTR)

End point title	Percent Change from Baseline in Magnetization Transfer Ratio

	(MTR)

End point description:

Magnetization Transfer Ratio (MTR) was measured using MRI technique. MRI cohort included subjects in the study 2008-004753-14 ITT population who had consented to participate in the MRI sub-study and have any MRI data in Studies 2006-003696-12,2006-003697-10or 2008-004753-14. Here, 'n' signifies number of subjects analysed at specific timepoint. Data for this endpoint was summarised as per the treatment received in previous studies (2006-003696-12 and 2006-003697-10).

End point type	Secondary

End point timeframe:

Baseline up to Week 288

End point values	BG00012 240 mg BID (Prior BG00012 240 mg BID)	BG00012 240 mg TID (Prior BG00012 240 mg TID)	BG00012 240 mg BID (Prior BG00012 Matched Placebo)	BG00012 240 mg TID (Prior BG00012 Matched Placebo)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	213	222	105	103
Units: percent change				
arithmetic mean (standard deviation)				
Change at Week 48 (n =126, 118, 49, 56, 20, 23)	-0.325 (± 5.4932)	-0.383 (± 4.8621)	1.034 (± 7.3548)	-0.567 (± 4.4766)
Change at Week 96 (n =118, 113, 46, 50, 20, 20)	-0.427 (± 6.6493)	-0.532 (± 4.9880)	1.630 (± 7.6584)	-0.947 (± 7.0771)
Change at Week 144 (n =103, 107, 45, 37, 19, 24)	-0.042 (± 9.2548)	0.509 (± 7.2692)	1.525 (± 8.6421)	1.411 (± 12.2825)
Change at Week 192 (n =100, 100, 42, 41, 25, 23)	1.038 (± 10.8680)	0.955 (± 8.6105)	3.012 (± 9.3831)	3.103 (± 13.0046)
Change at Week 240 (n =91, 90, 40, 42, 23, 20)	-0.002 (± 15.6190)	1.647 (± 8.3094)	3.213 (± 9.6621)	4.108 (± 13.8103)
Change at Week 288 (n =65, 71, 19, 25, 5, 14)	0.002 (± 4.0206)	-0.391 (± 4.6415)	-0.666 (± 2.0741)	-0.622 (± 2.2922)

End point values	BG00012 240 mg BID (Prior Glatiramer Acetate [GA])	BG00012 240 mg TID (Prior Glatiramer Acetate [GA])		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	49	60		
Units: percent change				
arithmetic mean (standard deviation)				
Change at Week 48 (n =126, 118, 49, 56, 20, 23)	-0.081 (± 13.6416)	-0.334 (± 1.5103)		
Change at Week 96 (n =118, 113, 46, 50, 20, 20)	-4.269 (± 12.6065)	0.215 (± 1.4270)		
Change at Week 144 (n =103, 107, 45, 37, 19, 24)	-4.460 (± 10.3887)	3.119 (± 8.1676)		
Change at Week 192 (n =100, 100, 42, 41, 25, 23)	1.384 (± 15.7611)	3.841 (± 10.8600)		
Change at Week 240 (n =91, 90, 40, 42, 23, 20)	2.959 (± 16.8386)	0.673 (± 25.9962)		
Change at Week 288 (n =65, 71, 19, 25, 5, 14)	-0.466 (± 0.9410)	-1.114 (± 2.4539)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Short Form-36 Health Survey (SF-36®) at Week 384

End point title	Change From Baseline in Short Form-36 Health Survey (SF-36®) at Week 384

End point description:

The SF-36 is a brief (36-item) scale reflecting the impact of both dysfunctions and general health perception the questionnaire measures: 1.physical function (PF),2. role physical (RF),3. bodily pain (BP),4. role emotional (RE),5. social function (SF), 6. general health (GH),7. vitality (VT), 8. mental health (MH). Items 1-4 primarily contribute to the PCS score of the SF-36. Items 5-8 primarily contribute to the mental component summary (MCS) score of the SF-36. The questions related to each dimension are scored on a scale from 0 (worst score) to 100 (best score), with higher scores indicating better function. ITT population included subjects who had entered study 2008-004753-14 and received at least one dose of study treatment. Here, 'n' signifies number of subjects analysed at specific timepoint. Data for this endpoint was summarised as per treatment received in previous studies (2006-003696-12 and 2006-003697-10).

End point type	Secondary

End point timeframe:

Baseline, Week 384

End point values	BG00012 240 mg BID (Prior BG00012 240 mg BID)	BG00012 240 mg TID (Prior BG00012 240 mg TID)	BG00012 240 mg BID (Prior BG00012 Matched Placebo)	BG00012 240 mg TID (Prior BG00012 Matched Placebo)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	501	502	249	248
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline: PF (n=494,487,244,240,115,112)	68.48 (± 25.938)	71.78 (± 24.849)	69.67 (± 24.481)	67.97 (± 26.279)
Change at Week 384: PF (n=236,215,90,97,43,48)	0.73 (± 21.972)	-4.79 (± 24.641)	-7.37 (± 22.253)	-6.89 (± 23.194)
Baseline: RF (n =494,486,244,238,114,112)	56.46 (± 41.254)	58.42 (± 41.280)	56.35 (± 40.896)	59.87 (± 41.747)
Change at Week 384: RF (n=232,215,90,94,43,48)	3.20 (± 48.259)	-2.75 (± 47.283)	-10.00 (± 43.188)	-8.24 (± 53.177)
Baseline: BP (n =494,490,244,240,115,112)	69.68 (± 25.587)	70.42 (± 24.688)	68.51 (± 26.163)	69.44 (± 26.016)
Change at Week 384: BP (n=237,216,90,97,43,48)	1.32 (± 28.525)	-1.47 (± 25.779)	-2.92 (± 23.486)	-4.36 (± 25.935)
Baseline: GH (n =493,489,240,238,115,110)	53.99 (± 21.563)	55.44 (± 20.768)	54.45 (± 18.690)	52.42 (± 20.028)
Change at Week 384: GH (n=234,213,86,95,42,47)	0.87 (± 18.744)	-2.12 (± 20.595)	-2.28 (± 16.752)	-0.52 (± 22.035)

Baseline: VT (n =492,486,242,239,115,111)	50.48 (± 20.966)	52.21 (± 19.842)	50.63 (± 19.130)	50.64 (± 21.069)
Change at Week 384: VT (n=235,214,87,96,41,47)	1.11 (± 19.857)	-0.73 (± 19.033)	-4.67 (± 17.934)	0.40 (± 20.822)
Baseline: SF (n =494,490,244,239,115,112)	71.46 (± 24.451)	71.53 (± 24.394)	69.67 (± 24.581)	72.23 (± 24.699)
Change at Week 384: SF (n=237,216,90,96,43,48)	-2.16 (± 25.575)	-3.30 (± 24.912)	-5.69 (± 22.184)	-2.08 (± 27.724)
Baseline: RE (n =491,485,241,238,115,111)	64.87 (± 40.653)	65.57 (± 40.015)	62.86 (± 42.715)	62.61 (± 41.280)
Change at Week 384: RE (n=233,214,90,96,43,47)	0.43 (± 49.950)	0.47 (± 43.513)	-12.22 (± 42.532)	4.17 (± 44.656)
Baseline: MH (n =492,486,242,239,115,111)	65.01 (± 19.818)	66.24 (± 19.060)	65.42 (± 17.658)	65.15 (± 19.233)
Change at Week 384: MH (n=235,214,87,96,41,47)	1.32 (± 19.715)	2.31 (± 18.095)	-3.91 (± 19.897)	2.33 (± 17.524)
Baseline:MCS(n=488,480,237,235,114,108)	45.40 (± 11.130)	45.63 (± 10.272)	45.13 (± 10.932)	45.31 (± 10.907)
Change at Week 384:MCS(n=226,211,85,92,41,45)	0.05 (± 12.415)	0.87 (± 10.028)	-2.55 (± 10.328)	1.97 (± 10.657)
Baseline:PCS(n=488,480,237,235,114,108)	43.53 (± 9.884)	44.44 (± 10.048)	43.74 (± 9.739)	43.56 (± 10.267)
Change at Week 384:PCS (n=226,211,85,92,41,45)	0.55 (± 9.373)	-1.94 (± 10.532)	-2.29 (± 8.929)	-3.25 (± 9.998)

End point values	BG00012 240 mg BID (Prior Glatiramer Acetate [GA])	BG00012 240 mg TID (Prior Glatiramer Acetate [GA])		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	118	118		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline: PF (n=494,487,244,240,115,112)	69.10 (± 25.226)	68.20 (± 25.370)		
Change at Week 384: PF (n=236,215,90,97,43,48)	-6.19 (± 21.719)	-6.25 (± 28.350)		
Baseline: RF (n =494,486,244,238,114,112)	55.26 (± 40.390)	53.57 (± 42.029)		
Change at Week 384: RF (n=232,215,90,94,43,48)	-12.21 (± 40.595)	-1.04 (± 54.568)		
Baseline: BP (n =494,490,244,240,115,112)	69.30 (± 25.766)	68.59 (± 26.102)		
Change at Week 384: BP (n=237,216,90,97,43,48)	-3.60 (± 22.138)	-4.46 (± 33.297)		
Baseline: GH (n =493,489,240,238,115,110)	51.21 (± 18.707)	52.58 (± 19.675)		
Change at Week 384: GH (n=234,213,86,95,42,47)	-5.64 (± 18.270)	1.21 (± 21.674)		
Baseline: VT (n =492,486,242,239,115,111)	51.30 (± 19.703)	50.33 (± 20.019)		
Change at Week 384: VT (n=235,214,87,96,41,47)	-6.71 (± 20.236)	1.03 (± 19.829)		
Baseline: SF (n =494,490,244,239,115,112)	69.02 (± 24.688)	69.53 (± 25.100)		
Change at Week 384: SF (n=237,216,90,96,43,48)	-10.76 (± 34.350)	-0.52 (± 25.780)		

Baseline: RE (n =491,485,241,238,115,111)	60.29 (± 41.393)	64.26 (± 41.854)		
Change at Week 384: RE (n=233,214,90,96,43,47)	-13.18 (± 42.501)	-3.55 (± 48.769)		
Baseline: MH (n =492,486,242,239,115,111)	62.30 (± 17.347)	63.61 (± 18.414)		
Change at Week 384: MH (n=235,214,87,96,41,47)	-0.29 (± 21.989)	-2.06 (± 20.066)		
Baseline:MCS(n=488,480,237,235,114,108)	44.00 (± 10.702)	45.03 (± 10.642)		
Change at Week 384:MCS(n=226,211,85,92,41,45)	-2.59 (± 12.895)	0.08 (± 10.328)		
Baseline:PCS(n=488,480,237,235,114,108)	43.68 (± 10.359)	43.15 (± 10.091)		
Change at Week 384:PCS (n=226,211,85,92,41,45)	-2.70 (± 8.860)	-1.59 (± 10.765)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in EuroQol 5 Dimensions Questionnaire (EQ-5D) Health Survey - EQ-5D Index Score at Week 384

End point title	Change From Baseline in EuroQol 5 Dimensions Questionnaire (EQ-5D) Health Survey - EQ-5D Index Score at Week 384

End point description:

The EQ-5D is a generic health-related quality of life instrument consisting of 2 components, EQ-5D index score and EQ-VAS. The EQ-5D provides a profile of the subject's health state in 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). For each dimension, the subject is instructed to indicate whether he or she has (1) "no problems", (2) "some problems", or (3) "severe problems". A positive change from baseline indicates improvement. ITT population included subjects who had entered study 2008-004753-14 and received at least one dose of study treatment. Here, 'n' signifies number of subjects analysed at specific timepoint. Data for this endpoint was summarised as per treatment received in previous studies (2006-003696-12 and 2006-003697-10).

End point type	Secondary

End point timeframe:

Baseline, Week 384

End point values	BG00012 240 mg BID (Prior BG00012 240 mg BID)	BG00012 240 mg TID (Prior BG00012 240 mg TID)	BG00012 240 mg BID (Prior BG00012 Matched Placebo)	BG00012 240 mg TID (Prior BG00012 Matched Placebo)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	501	502	249	248
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline (n =488, 484, 239, 239, 115, 112)	0.73 (± 0.210)	0.73 (± 0.222)	0.72 (± 0.223)	0.71 (± 0.244)
Change at Week 384 (n =230, 212, 86, 96, 42, 48)	0.01 (± 0.251)	0.00 (± 0.233)	-0.07 (± 0.269)	0.00 (± 0.249)

End point values	BG00012 240 mg BID (Prior Glatiramer Acetate [GA])	BG00012 240 mg TID (Prior Glatiramer Acetate [GA])		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	118	118		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline (n =488, 484, 239, 239, 115, 112)	0.71 (± 0.246)	0.72 (± 0.189)		
Change at Week 384 (n =230, 212, 86, 96, 42, 48)	-0.04 (± 0.253)	-0.03 (± 0.241)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in EuroQol 5 Dimensions Questionnaire (EQ-5D) Health Survey - Visual Analog Scale (VAS) at Week 384

End point title	Change From Baseline in EuroQol 5 Dimensions Questionnaire (EQ-5D) Health Survey - Visual Analog Scale (VAS) at Week 384

End point description:

The EQ-5D is a generic health-related quality of life instrument consisting of 2 components, EQ-5D index score and EQ-VAS. In EQ-VAS subjects are asked to rate their current health on a 20 centimetre (cm) scale from 0 to 100 where 0 represents "worst imaginable health state" and 100 represents "best imaginable health state". A positive change from baseline indicates improvement. ITT population included subjects who had entered study 2008-004753-14 and received at least one dose of study treatment. Here, 'n' signifies number of subjects analysed at specific timepoint. Data for this endpoint was summarised as per treatment received in previous studies (2006-003696-12 and 2006-003697-10).

End point type	Secondary

End point timeframe:

Baseline, Week 384

End point values	BG00012 240 mg BID (Prior BG00012 240 mg BID)	BG00012 240 mg TID (Prior BG00012 240 mg TID)	BG00012 240 mg BID (Prior BG00012 Matched Placebo)	BG00012 240 mg TID (Prior BG00012 Matched Placebo)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	501	502	249	248
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline (n =492, 488, 243, 238, 113, 112)	70.97 (± 18.460)	70.48 (± 19.993)	70.40 (± 17.630)	69.44 (± 19.907)
Change at Week 384 (n =235, 215, 91, 95, 42, 48)	-0.48 (± 19.631)	-1.67 (± 18.855)	-7.24 (± 18.419)	-3.17 (± 22.003)

End point values	BG00012 240 mg BID (Prior Glatiramer Acetate [GA])	BG00012 240 mg TID (Prior Glatiramer Acetate [GA])		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	118	118		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline (n =492, 488, 243, 238, 113, 112)	66.80 (± 18.846)	69.07 (± 20.094)		
Change at Week 384 (n =235, 215, 91, 95, 42, 48)	-1.71 (± 25.330)	-4.11 (± 16.270)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Visual Function Test Scores at Week 384

End point title	Change From Baseline in Visual Function Test Scores at Week 384

End point description:

Subjects were tested using the contrast level of 100%, 2.5%, and 1.25% charts, and the scores were defined as the number of letters identified correctly for each chart (the maximum score was 60). Higher scores indicate better functioning. A positive change from baseline indicates better functioning. ITT population included subjects who had entered study 2008-004753-14 and received at least one dose of study treatment. Here, 'n' signifies number of subjects analysed at specific timepoint. Data for this endpoint was summarised as per treatment received in previous studies (2006-003696-12 and 2006-003697-10).

End point type	Secondary

End point timeframe:

Baseline, Week 384

End point values	BG00012 240 mg BID (Prior BG00012 240 mg BID)	BG00012 240 mg TID (Prior BG00012 240 mg TID)	BG00012 240 mg BID (Prior BG00012 Matched Placebo)	BG00012 240 mg TID (Prior BG00012 Matched Placebo)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	501	502	249	248
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline:100%Chart (n=501,502,249,248,118,118)	54.7 (± 7.95)	55.0 (± 7.84)	55.1 (± 7.26)	54.8 (± 7.12)
Change at Week384:100%Chart(n=231,216,87,99	-0.4 (± 6.76)	-1.9 (± 6.81)	-1.4 (± 8.48)	-1.2 (± 7.53)
Baseline:2.5%Chart(n=501,502,249,248,118,118)	32.4 (± 12.17)	32.6 (± 11.76)	32.4 (± 11.42)	32.3 (± 11.99)
Change at Week384:2.5%Chart(n=231,216,87,99,	-2.4 (± 10.77)	-3.3 (± 10.43)	-1.5 (± 11.77)	-4.9 (± 11.14)

Baseline:1.25%Chart(n=501,502,249,248,118,118)	24.1 (± 12.45)	24.2 (± 12.28)	23.8 (± 12.11)	23.7 (± 12.96)
Change atWeek384:1.25%Chart(n=231,216,87,	-5.8 (± 13.39)	-6.0 (± 11.77)	-4.1 (± 13.04)	-7.4 (± 12.42)

End point values	BG00012 240 mg BID (Prior Glatiramer Acetate [GA])	BG00012 240 mg TID (Prior Glatiramer Acetate [GA])		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	118	118		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline:100%Chart (n=501,502,249,248,118,118)	54.3 (± 8.26)	55.0 (± 6.73)		
Change at Week384:100%Chart(n=231,216,87,99	-1.6 (± 8.05)	-0.7 (± 5.17)		
Baseline:2.5%Chart(n=501,502,249,248,118,118)	31.8 (± 12.36)	31.7 (± 12.41)		
Change at Week384:2.5%Chart(n=231,216,87,99,	-4.0 (± 11.90)	-2.1 (± 9.86)		
Baseline:1.25%Chart(n=501,502,249,248,118,118)	23.4 (± 11.76)	22.2 (± 13.25)		
Change atWeek384:1.25%Chart(n=231,216,87,	-6.7 (± 13.78)	-5.0 (± 12.74)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of the study up to follow-up (Day 1 up to Week 561)

Adverse event reporting additional description:

Safety population included all subjects who had any post-baseline safety follow-up in study 2008-004753-14, defined as any treatment emergent AE in study 2008-004753-14 or any post-baseline laboratory, vital signs, or physical exam assessment in study 2008-004753-14, and received at least one dose of study treatment in study 2008-004753-14.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.1

Reporting groups

Reporting group title	BG00012 240 mg BID

Reporting group description:

Subjects received BG00012 240 mg (120 mg each) capsules orally, BID and 2 matching placebo capsules QD up to 8 years.

Reporting group title	BG00012 240 mg TID

Reporting group description:

Subjects received BG00012 240 mg (120 mg each) capsules orally, TID up to 8 years.

Serious adverse events	BG00012 240 mg BID	BG00012 240 mg TID	
Total subjects affected by serious adverse events			
subjects affected / exposed	279 / 868 (32.14%)	272 / 868 (31.34%)	
number of deaths (all causes)	5	6	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenolymphoma			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal cancer			
subjects affected / exposed	2 / 868 (0.23%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			

subjects affected / exposed	3 / 868 (0.35%)	2 / 868 (0.23%)	
occurrences causally related to treatment / all	2 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign breast neoplasm			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign ovarian tumour			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bowenoid papulosis			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain cancer metastatic			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	4 / 868 (0.46%)	8 / 868 (0.92%)	
occurrences causally related to treatment / all	2 / 4	2 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer in situ			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer stage II			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast neoplasm			

subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carcinoid tumour of the pancreas			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervix neoplasm			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic myeloid leukaemia			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial cancer			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibroma			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glioma			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemangioma			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leiomyoma			

subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma stage II			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung squamous cell carcinoma stage unspecified			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	2 / 868 (0.23%)	2 / 868 (0.23%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningioma			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesothelioma malignant			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic malignant melanoma			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic neoplasm			
subjects affected / exposed	1 / 868 (0.12%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma			

subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal neoplasm benign			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal cancer			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma			
subjects affected / exposed	3 / 868 (0.35%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salivary gland cancer			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	1 / 868 (0.12%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of the cervix			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous endometrial carcinoma			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid cancer			

subjects affected / exposed	2 / 868 (0.23%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	6 / 868 (0.69%)	3 / 868 (0.35%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 868 (0.12%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			

subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Abdominoplasty			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve replacement			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicectomy			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder neck suspension			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bunion operation			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Caesarean section			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carpal tunnel decompression			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystectomy			

subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cochlea implant			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystocele repair			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Female sterilisation			
subjects affected / exposed	1 / 868 (0.12%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip arthroplasty			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hysterectomy			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Knee arthroplasty			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mammoplasty			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device change			

subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device removal			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cystectomy			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Percutaneous coronary intervention			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative care			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgery			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroidectomy			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia repair			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicose vein operation			

subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion missed			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abortion spontaneous			
subjects affected / exposed	1 / 868 (0.12%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complication of pregnancy			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Capsular contracture associated with breast implant			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait disturbance			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired healing			

subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 868 (0.00%)	3 / 868 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	3 / 868 (0.35%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Serositis			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Treatment failure			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug hypersensitivity			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			

Breast necrosis			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical dysplasia			
subjects affected / exposed	0 / 868 (0.00%)	2 / 868 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystocele			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysfunctional uterine bleeding			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial hyperplasia			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometriosis			
subjects affected / exposed	0 / 868 (0.00%)	3 / 868 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibrocystic breast disease			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Menorrhagia			
subjects affected / exposed	1 / 868 (0.12%)	2 / 868 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metrorrhagia			

subjects affected / exposed	1 / 868 (0.12%)	3 / 868 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst			
subjects affected / exposed	2 / 868 (0.23%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst ruptured			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic adhesions			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic pain			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine polyp			
subjects affected / exposed	1 / 868 (0.12%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Choking			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			

subjects affected / exposed	2 / 868 (0.23%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paranasal cyst			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary artery thrombosis			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 868 (0.23%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sarcoidosis			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Acute psychosis			

subjects affected / exposed	1 / 868 (0.12%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcoholism			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anorexia nervosa			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety disorder			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Burnout syndrome			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catatonia			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Completed suicide			
subjects affected / exposed	0 / 868 (0.00%)	2 / 868 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			

subjects affected / exposed	0 / 868 (0.00%)	3 / 868 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug abuse			
subjects affected / exposed	2 / 868 (0.23%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major depression			
subjects affected / exposed	0 / 868 (0.00%)	2 / 868 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mood disorder due to a general medical condition			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Morbid thoughts			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurosis			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric decompensation			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic behaviour			

subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder due to a general medical condition			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 868 (0.12%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary colic			
subjects affected / exposed	0 / 868 (0.00%)	2 / 868 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	3 / 868 (0.35%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			

subjects affected / exposed	1 / 868 (0.12%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis chronic			
subjects affected / exposed	0 / 868 (0.00%)	2 / 868 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	2 / 868 (0.23%)	7 / 868 (0.81%)	
occurrences causally related to treatment / all	0 / 2	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic hepatitis			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Anticoagulation drug level above therapeutic			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigation			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphocyte count decreased			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			

Accident			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Accident at work			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acetabulum fracture			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Animal bite			
subjects affected / exposed	0 / 868 (0.00%)	2 / 868 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	2 / 868 (0.23%)	2 / 868 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Avulsion fracture			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain contusion			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clavicle fracture			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Comminuted fracture			

subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	3 / 868 (0.35%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug toxicity			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	13 / 868 (1.50%)	18 / 868 (2.07%)	
occurrences causally related to treatment / all	0 / 16	0 / 19	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	3 / 868 (0.35%)	4 / 868 (0.46%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	3 / 868 (0.35%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula fracture			
subjects affected / exposed	0 / 868 (0.00%)	3 / 868 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			

subjects affected / exposed	2 / 868 (0.23%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand fracture			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 868 (0.12%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 868 (0.00%)	4 / 868 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incision site haematoma			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint injury			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint sprain			

subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament injury			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament rupture			
subjects affected / exposed	2 / 868 (0.23%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	1 / 868 (0.12%)	3 / 868 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus lesion			
subjects affected / exposed	1 / 868 (0.12%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple injuries			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle rupture			
subjects affected / exposed	0 / 868 (0.00%)	2 / 868 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			

subjects affected / exposed	2 / 868 (0.23%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative hernia			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pubis fracture			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	3 / 868 (0.35%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory fume inhalation disorder			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 868 (0.00%)	2 / 868 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	4 / 868 (0.46%)	5 / 868 (0.58%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skeletal injury			
subjects affected / exposed	1 / 868 (0.12%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			

subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic rupture			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	0 / 868 (0.00%)	2 / 868 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	1 / 868 (0.12%)	5 / 868 (0.58%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulna fracture			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Cytogenetic abnormality			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb malformation			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Acute coronary syndrome			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	2 / 868 (0.23%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 868 (0.00%)	2 / 868 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	2 / 868 (0.23%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve prolapse			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			

subjects affected / exposed	1 / 868 (0.12%)	5 / 868 (0.58%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wolff-parkinson-white syndrome			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular insufficiency			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervicobrachial syndrome			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complex partial seizures			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			

subjects affected / exposed	3 / 868 (0.35%)	2 / 868 (0.23%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disturbance in attention			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysarthria			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 868 (0.12%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia			
subjects affected / exposed	0 / 868 (0.00%)	2 / 868 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial aneurysm			

subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar radiculopathy			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	1 / 868 (0.12%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple sclerosis			
subjects affected / exposed	4 / 868 (0.46%)	2 / 868 (0.23%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple sclerosis relapse			
subjects affected / exposed	116 / 868 (13.36%)	122 / 868 (14.06%)	
occurrences causally related to treatment / all	3 / 229	9 / 217	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle spasticity			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
subjects affected / exposed	1 / 868 (0.12%)	2 / 868 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Optic neuritis			
subjects affected / exposed	0 / 868 (0.00%)	2 / 868 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			

subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraparesis			
subjects affected / exposed	2 / 868 (0.23%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parkinson's disease			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Quadriparesis			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiculitis			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Relapsing-remitting multiple sclerosis			
subjects affected / exposed	2 / 868 (0.23%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	1 / 868 (0.12%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			

subjects affected / exposed	2 / 868 (0.23%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient global amnesia			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trigeminal neuralgia			
subjects affected / exposed	1 / 868 (0.12%)	2 / 868 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uhthoff's phenomenon			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eosinophilia			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
subjects affected / exposed	2 / 868 (0.23%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphopenia			

subjects affected / exposed	1 / 868 (0.12%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 868 (0.12%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Hypoacusis			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden hearing loss			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo positional			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glaucoma			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal ischaemia			

subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulcerative keratitis			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vision blurred			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			
subjects affected / exposed	1 / 868 (0.12%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crohn's disease			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			

subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer perforation			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenitis			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	2 / 868 (0.23%)	3 / 868 (0.35%)	
occurrences causally related to treatment / all	2 / 2	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal inflammation			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal mucosal disorder			

subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal necrosis			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 868 (0.12%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 868 (0.12%)	3 / 868 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal haemorrhage			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			

subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	2 / 868 (0.23%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Volvulus			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis allergic			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Haematuria			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	1 / 868 (0.12%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 868 (0.12%)	2 / 868 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrotic syndrome			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurogenic bladder			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Autoimmune thyroiditis			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basedow's disease			
subjects affected / exposed	2 / 868 (0.23%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Goitre			

subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthyroidism			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	4 / 868 (0.46%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chondropathy			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot deformity			
subjects affected / exposed	2 / 868 (0.23%)	2 / 868 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc degeneration			

subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc disorder			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	5 / 868 (0.58%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myositis			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	5 / 868 (0.58%)	4 / 868 (0.46%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	1 / 868 (0.12%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periarthritis			

subjects affected / exposed	1 / 868 (0.12%)	3 / 868 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	2 / 868 (0.23%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed	2 / 868 (0.23%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal deformity			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondylolisthesis			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovitis			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	2 / 868 (0.23%)	4 / 868 (0.46%)	
occurrences causally related to treatment / all	0 / 2	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteriuria			

subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	0 / 868 (0.00%)	2 / 868 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	2 / 868 (0.23%)	2 / 868 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic sinusitis			
subjects affected / exposed	0 / 868 (0.00%)	2 / 868 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic tonsillitis			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue fever			
subjects affected / exposed	2 / 868 (0.23%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea infectious			

subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometritis			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia infection			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	2 / 868 (0.23%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis norovirus			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis rotavirus			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal bacterial infection			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Genital herpes			

subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma infection			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes simplex			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 868 (0.12%)	3 / 868 (0.35%)	
occurrences causally related to treatment / all	1 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected skin ulcer			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis viral			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal candidiasis			

subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral candidiasis			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papilloma viral infection			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic abscess			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonsillar abscess			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonsillitis			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	6 / 868 (0.69%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	1 / 7	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			

subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural infection			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculoma			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis chronic			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyothorax			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal abscess			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection viral			

subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scrub typhus			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	2 / 868 (0.23%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	10 / 868 (1.15%)	4 / 868 (0.46%)	
occurrences causally related to treatment / all	1 / 11	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			

subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal infection			
subjects affected / exposed	1 / 868 (0.12%)	0 / 868 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vestibular neuronitis			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 868 (0.12%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Progressive multifocal leukoencephalopathy (PML)			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 868 (0.12%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	1 / 868 (0.12%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 868 (0.00%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obesity			

subjects affected / exposed	2 / 868 (0.23%)	1 / 868 (0.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	BG00012 240 mg BID	BG00012 240 mg TID	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	779 / 868 (89.75%)	767 / 868 (88.36%)	
Vascular disorders			
Flushing			
subjects affected / exposed	170 / 868 (19.59%)	165 / 868 (19.01%)	
occurrences (all)	264	227	
Hot flush			
subjects affected / exposed	44 / 868 (5.07%)	53 / 868 (6.11%)	
occurrences (all)	62	71	
Hypertension			
subjects affected / exposed	51 / 868 (5.88%)	43 / 868 (4.95%)	
occurrences (all)	60	46	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	100 / 868 (11.52%)	102 / 868 (11.75%)	
occurrences (all)	126	139	
Pyrexia			
subjects affected / exposed	47 / 868 (5.41%)	43 / 868 (4.95%)	
occurrences (all)	62	55	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	54 / 868 (6.22%)	66 / 868 (7.60%)	
occurrences (all)	71	82	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	31 / 868 (3.57%)	46 / 868 (5.30%)	
occurrences (all)	37	54	
Depression			

subjects affected / exposed	102 / 868 (11.75%)	87 / 868 (10.02%)	
occurrences (all)	125	114	
Insomnia			
subjects affected / exposed	52 / 868 (5.99%)	51 / 868 (5.88%)	
occurrences (all)	59	59	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	53 / 868 (6.11%)	59 / 868 (6.80%)	
occurrences (all)	74	80	
Albumin urine present			
subjects affected / exposed	66 / 868 (7.60%)	62 / 868 (7.14%)	
occurrences (all)	107	86	
Lymphocyte count decreased			
subjects affected / exposed	56 / 868 (6.45%)	42 / 868 (4.84%)	
occurrences (all)	85	71	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	60 / 868 (6.91%)	63 / 868 (7.26%)	
occurrences (all)	113	108	
Nervous system disorders			
Dizziness			
subjects affected / exposed	60 / 868 (6.91%)	45 / 868 (5.18%)	
occurrences (all)	86	61	
Headache			
subjects affected / exposed	145 / 868 (16.71%)	131 / 868 (15.09%)	
occurrences (all)	247	205	
Hypoaesthesia			
subjects affected / exposed	64 / 868 (7.37%)	49 / 868 (5.65%)	
occurrences (all)	86	78	
Multiple sclerosis relapse			
subjects affected / exposed	324 / 868 (37.33%)	335 / 868 (38.59%)	
occurrences (all)	724	769	
Paraesthesia			
subjects affected / exposed	57 / 868 (6.57%)	59 / 868 (6.80%)	
occurrences (all)	78	72	
Blood and lymphatic system disorders			

Lymphopenia			
subjects affected / exposed	52 / 868 (5.99%)	42 / 868 (4.84%)	
occurrences (all)	83	59	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	50 / 868 (5.76%)	55 / 868 (6.34%)	
occurrences (all)	75	67	
Abdominal pain upper			
subjects affected / exposed	69 / 868 (7.95%)	76 / 868 (8.76%)	
occurrences (all)	90	108	
Diarrhoea			
subjects affected / exposed	111 / 868 (12.79%)	118 / 868 (13.59%)	
occurrences (all)	159	162	
Nausea			
subjects affected / exposed	56 / 868 (6.45%)	61 / 868 (7.03%)	
occurrences (all)	71	77	
Vomiting			
subjects affected / exposed	42 / 868 (4.84%)	45 / 868 (5.18%)	
occurrences (all)	52	54	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	47 / 868 (5.41%)	32 / 868 (3.69%)	
occurrences (all)	57	36	
Pruritus			
subjects affected / exposed	50 / 868 (5.76%)	38 / 868 (4.38%)	
occurrences (all)	61	50	
Rash			
subjects affected / exposed	45 / 868 (5.18%)	40 / 868 (4.61%)	
occurrences (all)	68	53	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	49 / 868 (5.65%)	61 / 868 (7.03%)	
occurrences (all)	71	90	
Microalbuminuria			
subjects affected / exposed	55 / 868 (6.34%)	61 / 868 (7.03%)	
occurrences (all)	78	103	
Proteinuria			

subjects affected / exposed	76 / 868 (8.76%)	81 / 868 (9.33%)	
occurrences (all)	108	127	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	97 / 868 (11.18%)	115 / 868 (13.25%)	
occurrences (all)	146	169	
Back pain			
subjects affected / exposed	125 / 868 (14.40%)	125 / 868 (14.40%)	
occurrences (all)	179	170	
Muscle spasms			
subjects affected / exposed	38 / 868 (4.38%)	49 / 868 (5.65%)	
occurrences (all)	46	78	
Musculoskeletal pain			
subjects affected / exposed	35 / 868 (4.03%)	49 / 868 (5.65%)	
occurrences (all)	42	59	
Pain in extremity			
subjects affected / exposed	102 / 868 (11.75%)	92 / 868 (10.60%)	
occurrences (all)	157	128	
Infections and infestations			
Bronchitis			
subjects affected / exposed	82 / 868 (9.45%)	98 / 868 (11.29%)	
occurrences (all)	121	150	
Gastroenteritis			
subjects affected / exposed	52 / 868 (5.99%)	33 / 868 (3.80%)	
occurrences (all)	65	40	
Herpes zoster			
subjects affected / exposed	47 / 868 (5.41%)	38 / 868 (4.38%)	
occurrences (all)	51	43	
Influenza			
subjects affected / exposed	87 / 868 (10.02%)	67 / 868 (7.72%)	
occurrences (all)	113	87	
Nasopharyngitis			
subjects affected / exposed	220 / 868 (25.35%)	226 / 868 (26.04%)	
occurrences (all)	564	528	
Pharyngitis			

subjects affected / exposed	44 / 868 (5.07%)	50 / 868 (5.76%)	
occurrences (all)	63	62	
Sinusitis			
subjects affected / exposed	65 / 868 (7.49%)	63 / 868 (7.26%)	
occurrences (all)	107	128	
Upper respiratory tract infection			
subjects affected / exposed	143 / 868 (16.47%)	136 / 868 (15.67%)	
occurrences (all)	296	253	
Urinary tract infection			
subjects affected / exposed	196 / 868 (22.58%)	164 / 868 (18.89%)	
occurrences (all)	394	319	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 September 2010	Extension of the duration of the study from 2 years to 5 years or marketing authorization (if approved), whichever occurs first.
17 March 2014	Extended the study duration for each subject from 5 years to 8 years and to change the dosing regimen from dose-blind dosing with BG00012 240 mg twice a day (BID) or three times a day (TID) to open-label dosing with BG00012 at a dose of 240 mg BID for all subjects.
02 September 2014	Updated the safety reporting information.
16 November 2014	Progressive multifocal leukoencephalopathy (PML) has occurred in the setting of severe, prolonged lymphopenia following BG00012 administration. Severe, prolonged lymphopenia is a known risk factor for PML. In the controlled and uncontrolled BG00012 clinical studies, 2% of subjects experienced lymphocyte counts <0.5*10^9 per litre (/L) for at least six months. In these subjects, the majority of lymphocyte counts remained <0.5*10^9/L with continued therapy. The study protocol is being amended to enable the early identification of subjects who are at risk for developing severe, prolonged lymphopenia, and to provide additional guidance on the management of such subjects.
21 January 2016	- Extended the study duration by an additional 4 years to collect data on long-term efficacy and safety of BG00012. - Increased the minimal duration of follow-up for lymphopenic subjects upon discontinuation of treatment with BG00012, per Committee for Medicinal Products for Human Use (CHMP) recommendations.
07 November 2016	Removed the discontinuation criteria of elevated serum creatinine (either >1.2*baseline serum creatinine or >1.2*upper limit of normal [ULN]), positive urinalysis, and low white blood cell (WBC) count.
05 February 2018	Changed the length of the study from 12 years to 8 years.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported