



Clinical trial results:

A multinational, multicenter, randomized, parallel-group study performed in subjects with Relapsing-Remitting Multiple Sclerosis (RRMS) to assess the efficacy, safety and tolerability of Glatiramer Acetate (GA) injection 40 mg administered three times a week compared to placebo in a double-blind design.

Summary

EudraCT number	2009-018084-27
Trial protocol	HU DE EE CZ LT BG IT GB
Global end of trial date	12 May 2017

Results information

Result version number	v1 (current)
This version publication date	06 November 2018
First version publication date	06 November 2018

Trial information

Trial identification

Sponsor protocol code	MS-GA-301
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01067521
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Teva Branded Pharmaceutical Products R&D, Inc
Sponsor organisation address	12 Hatrufa St., PO Box 8077, Sapir Industrial Zone, Netanya, Israel, 42504
Public contact	Senior Director, Clinical Development, Multiple Sclerosis, Teva Pharmaceuticals Industries Ltd., 001 888-483-8279, info.era-clinical@teva.de
Scientific contact	Senior Director, Clinical Development, Multiple Sclerosis, Teva Pharmaceuticals Industries Ltd., 001 888-483-8279, info.era-clinical@teva.de

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	12 April 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	12 May 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of Glatiramer Acetate (GA) injection 40 mg administered three times a week compared to placebo in subjects with RRMS, as measured by the number of confirmed relapses during the 12 months placebo controlled phase.

Assessment of safety and tolerability

Protection of trial subjects:

This study was conducted in full accordance with the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Consolidated Guideline (E6) and any applicable national and local laws and regulations.

Written and/or oral information about the study was provided to all subjects in a language understandable by the subjects. The information included an adequate explanation of the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force. Written informed consent was obtained from each subject before any study procedures or assessments were done. It was explained to the subjects that they were free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.

Each subject's willingness to participate in the study was documented in writing in an informed consent form (ICF) that was signed by the subject with the date of that signature indicated. Each investigator kept the original consent forms, and copies were given to the subjects.

Upon confirmed diagnosis of multiple sclerosis (MS) relapse (as defined in the protocol) or an increase in Kurtzke Expanded Disability Status Scale (EDSS) of 1.5 points or more, sustained for at least 3 months during the placebo-controlled (PC) phase of the study, the subjects were reminded of the standard-of-care medications available for the treatment of MS and provided the opportunity to terminate study participation. In these cases, the subjects were requested to sign a re-consent ICF if they chose to continue to participate in the study, in the same treatment assignment.

If the subjects did not sign the re-consent form following an MS relapse or an increase in EDSS of 1.5 points or more, sustained for at least 3 months during the PC phase of the study, their participation in the study was terminated.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 June 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 268
Country: Number of subjects enrolled	Romania: 145
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	Bulgaria: 214

Country: Number of subjects enrolled	Czech Republic: 18
Country: Number of subjects enrolled	Estonia: 14
Country: Number of subjects enrolled	Germany: 40
Country: Number of subjects enrolled	Hungary: 12
Country: Number of subjects enrolled	Italy: 16
Country: Number of subjects enrolled	Lithuania: 26
Country: Number of subjects enrolled	Israel: 3
Country: Number of subjects enrolled	Russian Federation: 166
Country: Number of subjects enrolled	Ukraine: 236
Country: Number of subjects enrolled	United States: 86
Country: Number of subjects enrolled	Croatia: 111
Country: Number of subjects enrolled	Georgia: 25
Country: Number of subjects enrolled	South Africa: 18
Worldwide total number of subjects	1404
EEA total number of subjects	870

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)	1404
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 1524 subjects were screened in this study, and 120 (7.9%) subjects failed screening. Of these, 69 did not meet inclusion or exclusion criteria, 30 withdrew from the study and 21 failed screening for other reasons.

Pre-assignment

Screening details:

1404 subjects were enrolled and randomized in the placebo-controlled (PC) double-blind period. Participants were randomized 2:1 to the treatment arms

Period 1

Period 1 title	Double-Blind Placebo-Controlled Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Blinding implementation details:

The Placebo-Controlled period was double blind. Subjects were randomly assigned to receive treatment with GA 40 mg sc TIW or placebo in a 2:1 ratio. The investigators, sponsor, and any personnel involved in subjects' assessment, monitoring, analysis, and data management (excluding the designated Clinical Supplies Unit [CSU] personnel), were blinded to the subject assignment. Treatment assignments were not to be recorded in any study documents or source document.

Arms

Are arms mutually exclusive?	Yes
Arm title	Early Start: GA 40 mg / GA 40 mg

Arm description:

Participants were administered glatiramer acetate (GA) 40 mg/mL by subcutaneous injection three times a week for 12 months during the double-blind Placebo-Controlled Period, and then continued that treatment in the Open-label Period from Month 13 up to Year 6.5 until the study ended.

Arm type	Experimental
Investigational medicinal product name	glatiramir acetate
Investigational medicinal product code	
Other name	GA, Copaxone
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

GA 40 mg/mL for subcutaneous injection in a pre-filled syringe (PFS) administered three times a week. Each PFS also contained 40 mg of mannitol dissolved in water for injection.

Arm title	Delayed Start: Placebo / GA 40 mg
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Arm description:

Participants were administered placebo subcutaneous injections three times a week for 12 months during the double-blind Placebo-Controlled Period. Participants were then switched to glatiramer acetate (GA) 40 mg/mL by subcutaneous injection three times a week during the Open-Label Period from Month 13 up to Year 6.5 until the study ended.

Arm type	Placebo
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Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Matching placebo for subcutaneous injection (40 mg of mannitol dissolved in 1 mL of water for injection) in a pre-filled syringe (PFS) administered three times a week for 12 months during the Placebo-Controlled period.

Investigational medicinal product name	glatiramer acetate
Investigational medicinal product code	
Other name	GA, Copaxone
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

GA 40 mg/mL for subcutaneous injection in a pre-filled syringe (PFS) administered three times a week during the Open-Label period which started at Month 13 and continued up to Year 6.5 until the study ended. Each PFS also contained 40 mg of mannitol dissolved in water for injection.

Number of subjects in period 1	Early Start: GA 40 mg / GA 40 mg	Delayed Start: Placebo / GA 40 mg
Started	943	461
Completed	859	430
Not completed	84	31
Adverse event, serious fatal	-	1
Consent withdrawn by subject	34	17
Physician decision	1	1
Adverse event, non-fatal	29	6
Refuse to sign informed consent	4	1
Pregnancy	7	4
Non-compliance with study drug	2	-
Lost to follow-up	5	1
Protocol deviation	2	-

Period 2

Period 2 title	Open-Label Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
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Arm title	Early Start: GA 40 mg / GA 40 mg
Arm description: Participants were administered glatiramer acetate (GA) 40 mg/mL by subcutaneous injection three times a week for 12 months during the double-blind Placebo-Controlled Period, and then continued that treatment in the Open-Label Period from Month 13 up to Year 6.5 until the study ended.	
Arm type	Experimental
Investigational medicinal product name	glatiramir acetate
Investigational medicinal product code	
Other name	GA, Copaxone
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

GA 40 mg/mL for subcutaneous injection in a pre-filled syringe (PFS) administered three times a week. Each PFS also contained 40 mg of mannitol dissolved in water for injection.

Arm title	Delayed Start: Placebo / GA 40 mg
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Arm description:

Participants were administered placebo subcutaneous injections three times a week for 12 months during the double-blind Placebo-Controlled Period. Participants were then switched to glatiramer acetate (GA) 40 mg/mL by subcutaneous injection three times a week during the Open-Label Period from Month 13 up to Year 6.5 until the study ended.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Matching placebo for subcutaneous injection (40 mg of mannitol dissolved in 1 mL of water for injection) in a pre-filled syringe (PFS) administered three times a week for 12 months during the Placebo-Controlled period.

Investigational medicinal product name	glatiramir acetate
Investigational medicinal product code	
Other name	GA, Copaxone
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

GA 40 mg/mL for subcutaneous injection in a pre-filled syringe (PFS) administered three times a week during the Open-Label period which started at Month 13 and continued up to Year 6.5 until the study ended. Each PFS also contained 40 mg of mannitol dissolved in water for injection.

Number of subjects in period 2^[1]	Early Start: GA 40 mg / GA 40 mg	Delayed Start: Placebo / GA 40 mg
Started	834	419
Completed	580	261
Not completed	254	158
Adverse event, serious fatal	3	1
Consent withdrawn by subject	160	88
Physician decision	13	11
Adverse event, non-fatal	30	28

Pregnancy	14	8
Non-compliance with study drug	5	-
Lost to follow-up	21	20
Teva requested subject to be withdrawn	5	2
Protocol deviation	3	-

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Some participants did not continue into the open-label period.

Baseline characteristics

Reporting groups

Reporting group title	Early Start: GA 40 mg / GA 40 mg
Reporting group description:	
Participants were administered glatiramer acetate (GA) 40 mg/mL by subcutaneous injection three times a week for 12 months during the double-blind Placebo-Controlled Period, and then continued that treatment in the Open-label Period from Month 13 up to Year 6.5 until the study ended.	
Reporting group title	Delayed Start: Placebo / GA 40 mg
Reporting group description:	
Participants were administered placebo subcutaneous injections three times a week for 12 months during the double-blind Placebo-Controlled Period. Participants were then switched to glatiramer acetate (GA) 40 mg/mL by subcutaneous injection three times a week during the Open-Label Period from Month 13 up to Year 6.5 until the study ended.	

Reporting group values	Early Start: GA 40 mg / GA 40 mg	Delayed Start: Placebo / GA 40 mg	Total
Number of subjects	943	461	1404
Age categorical			
Units: Subjects			
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	943	461	1404
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	37.36	38.12	
standard deviation	± 9.401	± 9.222	-
Gender categorical			
Units: Subjects			
Female	641	313	954
Male	302	148	450
Race			
Units: Subjects			
American Indian or Alaska Native	1	0	1
Asian	2	0	2
Black or African American	12	3	15
Other	12	3	15
White	916	455	1371
Ethnicity			
Units: Subjects			
Not Hispanic or Latino	934	460	1394
Hispanic or Latino	9	1	10
Body Mass Index			
Units: kg/m ²			
arithmetic mean	24.38	24.44	
standard deviation	± 4.709	± 4.804	-
Time from First Symptom			
Units: years			
arithmetic mean	7.68	7.61	
standard deviation	± 6.748	± 6.360	-

Time from Multiple Sclerosis (MS) Diagnosis Units: years arithmetic mean standard deviation	3.70 ± 4.982	3.88 ± 4.744	-
Number of T1 Gadolinium (Gd)-Enhanced Lesions per Participant at Baseline Units: lesions arithmetic mean standard deviation	1.7 ± 4.70	1.4 ± 3.69	-
Number of T2 Lesions Per Participant at Baseline Units: lesions arithmetic mean standard deviation	38.9 ± 26.34	36.7 ± 26.68	-
Sienax Normalized Brain Volume at Baseline			
Sienax estimates total brain tissue volume, from a single image, normalised for skull size. One participant in the GA40 mg ('Early Start') arm was missing the Sienax normalized brain volume baseline measure.			
Units: mL arithmetic mean standard deviation	1533.888 ± 110.6107	1537.899 ± 110.7549	-

End points

End points reporting groups

Reporting group title	Early Start: GA 40 mg / GA 40 mg
Reporting group description: Participants were administered glatiramer acetate (GA) 40 mg/mL by subcutaneous injection three times a week for 12 months during the double-blind Placebo-Controlled Period, and then continued that treatment in the Open-label Period from Month 13 up to Year 6.5 until the study ended.	
Reporting group title	Delayed Start: Placebo / GA 40 mg
Reporting group description: Participants were administered placebo subcutaneous injections three times a week for 12 months during the double-blind Placebo-Controlled Period. Participants were then switched to glatiramer acetate (GA) 40 mg/mL by subcutaneous injection three times a week during the Open-Label Period from Month 13 up to Year 6.5 until the study ended.	
Reporting group title	Early Start: GA 40 mg / GA 40 mg
Reporting group description: Participants were administered glatiramer acetate (GA) 40 mg/mL by subcutaneous injection three times a week for 12 months during the double-blind Placebo-Controlled Period, and then continued that treatment in the Open-Label Period from Month 13 up to Year 6.5 until the study ended.	
Reporting group title	Delayed Start: Placebo / GA 40 mg
Reporting group description: Participants were administered placebo subcutaneous injections three times a week for 12 months during the double-blind Placebo-Controlled Period. Participants were then switched to glatiramer acetate (GA) 40 mg/mL by subcutaneous injection three times a week during the Open-Label Period from Month 13 up to Year 6.5 until the study ended.	
Subject analysis set title	Entire Study: Early Start: GA 40 mg / GA 40 mg
Subject analysis set type	Intention-to-treat
Subject analysis set description: Participants were administered glatiramer acetate (GA) 40 mg/mL by subcutaneous injection three times a week for 12 months during the double-blind Placebo-Controlled Period, and then continued that treatment in the Open-label Period from Month 13 up to Year 6.5 until the study ended.	
Subject analysis set title	Entire Study: Delayed Start: Placebo / GA 40 mg
Subject analysis set type	Intention-to-treat
Subject analysis set description: Participants were administered placebo subcutaneous injections three times a week for 12 months during the double-blind Placebo-Controlled Period. Participants were then switched to glatiramer acetate (GA) 40 mg/mL by subcutaneous injection three times a week during the Open-Label Period from Month 13 up to Year 6.5 until the study ended.	
Subject analysis set title	OL Period - Delayed Start: GA 40 mg
Subject analysis set type	Safety analysis
Subject analysis set description: After completing the double-blind Placebo-Controlled Period, participants had the option of continuing in the study on open-label glatiramer acetate (GA) 40 mg/ml by subcutaneous injection three times a week until the study ended. This 'Delayed Start' treatment began at Month 13 and continued until the study ended (up to about 6.5 years).	
Subject analysis set title	PC Period-Delayed Start: Placebo
Subject analysis set type	Safety analysis
Subject analysis set description: Participants were administered placebo subcutaneous injections three times a week from Day 1 to Month 12 during the double-blind Placebo-Controlled Period.	

Primary: Total Number of Confirmed Relapses During the Placebo Controlled (PC) Treatment Period Estimated by Negative Binomial Regression

End point title	Total Number of Confirmed Relapses During the Placebo Controlled (PC) Treatment Period Estimated by Negative Binomial Regression
End point description: Relapses were monitored throughout the study. During the PC Period, two neurologists/physicians assessed subjects' general medical and neurological evaluations separately. A relapse was defined as the appearance of 1+ new neurological abnormalities or the reappearance of 1+ previously observed neurological abnormalities lasting ≥ 48 hours and immediately preceded by an improving neurological state of at ≥ 30 days from onset of previous relapse. An event was counted as a relapse only when the subject's symptoms were accompanied by observed objective neurological changes, consistent with \geq one of the following: - An increase of ≥ 0.5 in the Expanded Disability Status Scale (EDSS) score as compared to previous evaluation. - An increase of one grade in the actual score of ≥ 2 of the 7 functional systems (FS), as compared to previous evaluation. - An increase of 2 grades in the actual score of one FS as compared to the previous evaluation. Adjusted mean values are displayed.	
End point type	Primary
End point timeframe: Day 1 to 12 months	

End point values	Early Start: GA 40 mg / GA 40 mg	Delayed Start: Placebo / GA 40 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	943 ^[1]	461 ^[2]		
Units: confirmed relapses				
arithmetic mean (standard error)	0.331 (\pm 0.028)	0.505 (\pm 0.049)		

Notes:

[1] - Intent To Treat (ITT) Analysis Population

[2] - Intent To Treat (ITT) Analysis Population

Statistical analyses

Statistical analysis title	Number of Confirmed Relapses During PC Period
Statistical analysis description: Relapses were estimated by a baseline-adjusted, Negative Binomial Regression with an "offset" based on the log of subject's exposure to treatment. The model included the following covariates: - Baseline EDSS score. - Log of the prior 2-year number of relapses. - Volume of T2 lesions at baseliner. - Status of Gd-enhancing T1 activity at baseline (=0 no Gd-enhancing T1 at baseline; =1 at least one Gd-enhancing T1 at baseline). - CGR.	
Comparison groups	Delayed Start: Placebo / GA 40 mg v Early Start: GA 40 mg / GA 40 mg

Number of subjects included in analysis	1404
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Negative binomial regression model
Parameter estimate	Risk ratio (RR)
Point estimate	0.656
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.539
upper limit	0.799
Variability estimate	Standard error of the mean
Dispersion value	0.066

Notes:

[3] - The overall significance level for this study is 5%.

Primary: Annualized Rate of Confirmed Relapses Comparing Early Starters to Delayed Starters Estimated by Negative Binomial Regression

End point title	Annualized Rate of Confirmed Relapses Comparing Early Starters to Delayed Starters Estimated by Negative Binomial Regression
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End point description:

The annualized relapse rate (ARR) was calculated for the study by dividing the cumulative number of confirmed relapses by the number of person-years of exposure to treatment. The analysis of the annualized relapse rate is based on estimating a contrast (early start vs delayed start) derived from a baseline-adjusted, Negative Binomial Regression model to the number of confirmed relapses observed during study (post randomization) with an "offset" based on the log of exposure to treatment.

End point type	Primary
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End point timeframe:

Day 1 up to 6.5 years

End point values	Entire Study: Early Start: GA 40 mg / GA 40 mg	Entire Study: Delayed Start: Placebo / GA 40 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	943	461		
Units: relapses per year				
arithmetic mean (standard error)	0.2621 (± 0.0189)	0.3146 (± 0.0279)		

Statistical analyses

Statistical analysis title	Annualized Rate of Relapse
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Statistical analysis description:

Entire Study The Negative Binomial Regression model covariates:

- treatment group
- PCBL (Placebo-Controlled Baseline) Kurtzke's Expanded Disability Status Scale (EDSS) score as 1 degree of freedom variable
- Log of the # of relapses in the 2 years prior to PCBL
- Volume of T2 lesions at PCBL
- Status of Gd-enhancing T1 lesion activity at PCBL (=0 if no Gd-enhancing T1 lesions at PCBL; =1 if at least one Gd-enhancing T1 lesion at PCBL)
- Country or Geographical Region (CGR)

Comparison groups	Entire Study: Early Start: GA 40 mg / GA 40 mg v Entire Study: Delayed Start: Placebo / GA 40 mg
Number of subjects included in analysis	1404
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0409 ^[4]
Method	Negative binomial regression model
Parameter estimate	Risk ratio (RR)
Point estimate	0.8332
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6995
upper limit	0.9925
Variability estimate	Standard error of the mean
Dispersion value	0.0744

Notes:

[4] - not adjusted for multiplicity

Secondary: The Cumulative Number of New/Enlarging T2 Lesions Taken at Month 6 and Month 12 During the Placebo Controlled (PC) Treatment Period Estimated by Negative Binomial Regression

End point title	The Cumulative Number of New/Enlarging T2 Lesions Taken at Month 6 and Month 12 During the Placebo Controlled (PC) Treatment Period Estimated by Negative Binomial Regression
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End point description:

T2 lesions are hyperintense brain lesions that show on magnetic resonance imaging (MRI) and are associated with multiple sclerosis. The cumulative number of T2 lesions at Months 6 and 12 that are new or enlarged as compared to the baseline MRI are offered. Note that the two timeframes (Months 6 and 12) are combined.

Adjusted mean is based on negative binomial regression, adjusted for baseline number of T2 lesions and country or geographical region as covariates.

When a subject had both Month 6 and Month 12 scans missing, the subject was excluded from the analysis. When the Month 12 scan was missing, data from Month 6 was used and an offset of log (0.5) introduced. When the Month 6 scan was missing, data from Month 12 was used with an offset of 0.

End point type	Secondary
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End point timeframe:

Baseline (Day -7), Month 6, Month 12

End point values	Early Start: GA 40 mg / GA 40 mg	Delayed Start: Placebo / GA 40 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	884 ^[5]	441 ^[6]		
Units: lesions				
arithmetic mean (standard error)	3.650 (± 0.259)	5.592 (± 0.490)		

Notes:

[5] - ITT. See outcome description for how missing data was handled.

[6] - ITT. See outcome description for how missing data was handled.

Statistical analyses

Statistical analysis title	Cumulative # New-Enlarged T2 Lesions
Statistical analysis description:	
Negative binomial regression	
Comparison groups	Early Start: GA 40 mg / GA 40 mg v Delayed Start: Placebo / GA 40 mg
Number of subjects included in analysis	1325
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[7]
Method	Negative binomial regression model
Parameter estimate	Risk ratio (RR)
Point estimate	0.653
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.546
upper limit	0.78
Variability estimate	Standard error of the mean
Dispersion value	0.059

Notes:

[7] - The overall significance level for this study is 5%

Secondary: The Cumulative Number of Gadolinium (Gd)-Enhanced Lesions on T1-Weighted Images At Month 6 and Month 12 of the Placebo-Controlled (PC) Treatment Period Estimated by Negative Binomial Regression

End point title	The Cumulative Number of Gadolinium (Gd)-Enhanced Lesions on T1-Weighted Images At Month 6 and Month 12 of the Placebo-Controlled (PC) Treatment Period Estimated by Negative Binomial Regression
End point description:	
<p>The cumulative number of gadolinium (Gd)-enhanced lesions on T1-weighted images at Months 6 and 12 as compared to the baseline MRI are offered. Note that the two timeframes (Months 6 and 12) are combined.</p> <p>Adjusted mean is based on negative binomial regression with an "offset" employing the log of the proportion of the number of the available post-baseline scans to adjust for missing MRI scans (if any), adjusted for baseline number of enhancing lesions on T1-weighted images and country or geographical region as covariates. When a subject had both Month 6 and Month 12 scans missing, the subject was excluded from the analysis.</p>	
End point type	Secondary

End point timeframe:

Baseline (Day -7), Month 6, Month 12

End point values	Early Start: GA 40 mg / GA 40 mg	Delayed Start: Placebo / GA 40 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	884 ^[8]	441 ^[9]		
Units: lesions				
arithmetic mean (standard error)	0.905 (± 0.087)	1.639 (± 0.194)		

Notes:

[8] - ITT. See outcome description for how missing data was handled.

[9] - ITT. See outcome description for how missing data was handled.

Statistical analyses

Statistical analysis title	Cumulative # of Enhanced T1 Lesions
Comparison groups	Delayed Start: Placebo / GA 40 mg v Early Start: GA 40 mg / GA 40 mg
Number of subjects included in analysis	1325
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[10]
Method	Negative binomial regression model
Parameter estimate	Risk ratio (RR)
Point estimate	0.552
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.436
upper limit	0.699
Variability estimate	Standard error of the mean
Dispersion value	0.066

Notes:

[10] - The overall significance level for this study is 5%

Secondary: Brain Atrophy As Defined by the Percent of Change in Normalized Brain Volume From Baseline to Month 12 During the Placebo Controlled (PC) Treatment Period

End point title	Brain Atrophy As Defined by the Percent of Change in Normalized Brain Volume From Baseline to Month 12 During the Placebo Controlled (PC) Treatment Period
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End point description:

The analysis of brain atrophy as defined by the percentage change in normalized brain volume from baseline to Month 12 was based on the outcome of a contrast (GA 40 mg TIW vs. placebo) derived from a baseline-adjusted ANCOVA.

In addition to the treatment group, the model included the following covariates:

- SIENAX normalized brain volume at baseline.
- The number of enhancing lesions on T1-weighted images at baseline.
- country or geographical region.

Sienax estimates total brain tissue volume, from a single image, normalised for skull size.

End point type	Secondary
End point timeframe:	
Baseline (Day -7), Month 12	

End point values	Early Start: GA 40 mg / GA 40 mg	Delayed Start: Placebo / GA 40 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	840 ^[11]	423 ^[12]		
Units: percentage change				
arithmetic mean (standard error)	-0.706 (\pm 0.037)	-0.645 (\pm 0.047)		

Notes:

[11] - ITT population of participants who had SIENEX brain volume estimates at both baseline and Month 12.

[12] - ITT population of participants who had SIENEX brain volume estimates at both baseline and Month 12.

Statistical analyses

Statistical analysis title	% Change in Normalized Brain Volume
Comparison groups	Early Start: GA 40 mg / GA 40 mg v Delayed Start: Placebo / GA 40 mg
Number of subjects included in analysis	1263
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2058 ^[13]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.061
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.154
upper limit	0.033
Variability estimate	Standard error of the mean
Dispersion value	0.048

Notes:

[13] - The overall significance level for this study is 5%

Secondary: The Number of New/Enlarging T2 Lesions at Months 6, 12 and 36 Estimated by Negative Binomial Regression

End point title	The Number of New/Enlarging T2 Lesions at Months 6, 12 and 36 Estimated by Negative Binomial Regression
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End point description:

All data accumulated from screening, the PC Treatment period up to the end of the Open Label (OL) period are combined and referred to as the Long Term Period.

T2 lesions are hyperintense brain lesions that show on magnetic resonance imaging (MRI) and are associated with multiple sclerosis. The number of T2 lesions at Months 6, 12 and 36 that are new or enlarged as compared to the baseline MRI are offered. Adjusted mean is based on negative binomial regression, adjusted for baseline number of T2 lesions and country or geographical region as covariates. An "offset" employing the log of the proportion of the number of the available post-placebo-controlled

baseline (PCBL) scans was used to adjust for missing MRI scans.

End point type	Secondary
End point timeframe:	
Baseline (Day -7), Month 6, Month 12, Month 36	

End point values	Entire Study: Early Start: GA 40 mg / GA 40 mg	Entire Study: Delayed Start: Placebo / GA 40 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	883 ^[14]	440 ^[15]		
Units: lesions				
arithmetic mean (standard error)				
Month 6 (n=883, 440)	2.872 (± 0.214)	3.902 (± 0.43)		
Month 12 (n=854, 425)	4.484 (± 0.318)	7.086 (± 0.699)		
Month 36 (n=571, 263)	5.836 (± 0.41)	8.759 (± 0.82)		

Notes:

[14] - ITT population of participants with MRIs at both baseline and the designated timeframes.

[15] - ITT population of participants with MRIs at both baseline and the designated timeframes.

Statistical analyses

Statistical analysis title	Month 6
Statistical analysis description:	
Negative binomial regression n=1323	
Comparison groups	Entire Study: Early Start: GA 40 mg / GA 40 mg v Entire Study: Delayed Start: Placebo / GA 40 mg
Number of subjects included in analysis	1323
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0056 ^[16]
Method	Negative binomial regression model
Parameter estimate	Risk ratio (RR)
Point estimate	0.736
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.592
upper limit	0.914
Variability estimate	Standard error of the mean
Dispersion value	0.081

Notes:

[16] - not adjusted for multiplicity

Statistical analysis title	Month 12
Statistical analysis description:	
Negative binomial regression n=1279	

Comparison groups	Entire Study: Early Start: GA 40 mg / GA 40 mg v Entire Study: Delayed Start: Placebo / GA 40 mg
Number of subjects included in analysis	1323
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[17]
Method	Negative binomial regression model
Parameter estimate	Risk ratio (RR)
Point estimate	0.633
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.524
upper limit	0.765
Variability estimate	Standard error of the mean
Dispersion value	0.061

Notes:

[17] - not adjusted for multiplicity

Statistical analysis title	Month 36
Statistical analysis description: Negative binomial regression n=834	
Comparison groups	Entire Study: Early Start: GA 40 mg / GA 40 mg v Entire Study: Delayed Start: Placebo / GA 40 mg
Number of subjects included in analysis	1323
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[18]
Method	Negative binomial regression model
Parameter estimate	Risk ratio (RR)
Point estimate	0.666
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.557
upper limit	0.797
Variability estimate	Standard error of the mean
Dispersion value	0.061

Notes:

[18] - not adjusted for multiplicity

Secondary: The Cumulative Number of Gadolinium (Gd)-Enhanced Lesions on T1-Weighted Images At Months 6, 12 and 36 Estimated by Negative Binomial Regression

End point title	The Cumulative Number of Gadolinium (Gd)-Enhanced Lesions on T1-Weighted Images At Months 6, 12 and 36 Estimated by Negative Binomial Regression
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End point description:

All data accumulated from screening, the PC Treatment period up to the end of the Open Label (OL) period are combined and referred to as the Long Term Period. The cumulative number of gadolinium (Gd)-enhanced lesions on

T1-weighted images at Months 6, 12 and 36 as compared to the baseline MRI are offered. Adjusted mean is based on negative binomial regression. The model was fit using an autoregressive covariance structure. Covariates used: number of enhancing lesions on T1-weighted images at placebo-controlled baseline and country or geographical region. The cumulative number is derived from all the data points before it. For example, if the participant skipped one time point in between the baseline and 36 months, then it cannot be calculated.

End point type	Secondary
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End point timeframe:

Baseline (Day -7), Month 6, Month 12, Month 36

End point values	Entire Study: Early Start: GA 40 mg / GA 40 mg	Entire Study: Delayed Start: Placebo / GA 40 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	883 ^[19]	440 ^[20]		
Units: lesions				
arithmetic mean (standard error)				
Month 6 (n=883, 440)	0.629 (± 0.072)	1.131 (± 0.186)		
Month 12 (n=854, 425)	1.054 (± 0.115)	2.051 (± 0.282)		
Month 36 (n=570, 263)	1.501 (± 0.168)	2.265 (± 0.278)		

Notes:

[19] - ITT; participants with MRIs at baseline + timeframes, inclusive of proceeding post-baseline times.

[20] - ITT; participants with MRIs at baseline + timeframes, inclusive of proceeding post-baseline times.

Statistical analyses

Statistical analysis title	Month 6
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Statistical analysis description:

n=1323

Comparison groups	Entire Study: Early Start: GA 40 mg / GA 40 mg v Entire Study: Delayed Start: Placebo / GA 40 mg
Number of subjects included in analysis	1323
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0005 ^[21]
Method	Negative binomial regression model
Parameter estimate	Risk ratio (RR)
Point estimate	0.556
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	0.773
Variability estimate	Standard error of the mean
Dispersion value	0.093

Notes:

[21] - not adjusted for multiplicity

Statistical analysis title	Month 12
Statistical analysis description: n=1279	
Comparison groups	Entire Study: Early Start: GA 40 mg / GA 40 mg v Entire Study: Delayed Start: Placebo / GA 40 mg
Number of subjects included in analysis	1323
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[22]
Method	Negative binomial regression model
Parameter estimate	Risk ratio (RR)
Point estimate	0.514
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.388
upper limit	0.679
Variability estimate	Standard error of the mean
Dispersion value	0.073

Notes:

[22] - not adjusted for multiplicity

Statistical analysis title	Month 36
Statistical analysis description: n=833	
Comparison groups	Entire Study: Early Start: GA 40 mg / GA 40 mg v Entire Study: Delayed Start: Placebo / GA 40 mg
Number of subjects included in analysis	1323
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0015 ^[23]
Method	Negative binomial regression model
Parameter estimate	Risk ratio (RR)
Point estimate	0.663
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.514
upper limit	0.854
Variability estimate	Standard error of the mean
Dispersion value	0.086

Notes:

[23] - not adjusted for multiplicity

Secondary: Brain Atrophy As Defined by the Percent of Change in Brain Volume From Baseline to Months 6, 12 and 36 Estimated by a Mixed Model for Repeated Measures

End point title	Brain Atrophy As Defined by the Percent of Change in Brain
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End point description:

The analysis of brain atrophy as defined by the percentage change in brain volume from baseline to Months 6, 12 and 36 was performed using mixed model for repeated measures (MMRM) with SIENAX normalized brain volume at baseline, number of Gd-enhancing lesions at baseline, and country or geographical region as fixed effects.

Sienax estimates total brain tissue volume, from a single image, normalised for skull size.

End point type Secondary

End point timeframe:

Baseline (Day -7), Month 6, Month 12, Month 36

End point values	Entire Study: Early Start: GA 40 mg / GA 40 mg	Entire Study: Delayed Start: Placebo / GA 40 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	872 ^[24]	436 ^[25]		
Units: percentage change				
arithmetic mean (standard error)				
Month 6 (n=872, 436)	-0.429 (± 0.032)	-0.345 (± 0.04)		
Month 12 (n=846, 423)	-0.739 (± 0.035)	-0.653 (± 0.046)		
Month 36 (n=543, 250)	-1.935 (± 0.063)	-1.952 (± 0.09)		

Notes:

[24] - ITT population; participants with SIENEX brain scans at both baseline and the designated timeframes.

[25] - ITT population; participants with SIENEX brain scans at both baseline and the designated timeframes.

Statistical analyses

Statistical analysis title	Month 6
Statistical analysis description:	
n=1308	
Comparison groups	Entire Study: Early Start: GA 40 mg / GA 40 mg v Entire Study: Delayed Start: Placebo / GA 40 mg
Number of subjects included in analysis	1308
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0425 ^[26]
Method	mixed model for repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-0.084
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.166
upper limit	-0.003

Variability estimate	Standard error of the mean
Dispersion value	0.041

Notes:

[26] - not adjusted for multiplicity

Statistical analysis title	Month 12
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Statistical analysis description:

n=1269

Comparison groups	Entire Study: Early Start: GA 40 mg / GA 40 mg v Entire Study: Delayed Start: Placebo / GA 40 mg
Number of subjects included in analysis	1308
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0844 ^[27]
Method	mixed model for repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-0.086
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.184
upper limit	0.012
Variability estimate	Standard error of the mean
Dispersion value	0.05

Notes:

[27] - not adjusted for multiplicity

Statistical analysis title	Month 36
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Statistical analysis description:

n=793

Comparison groups	Entire Study: Early Start: GA 40 mg / GA 40 mg v Entire Study: Delayed Start: Placebo / GA 40 mg
Number of subjects included in analysis	1308
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8701 ^[28]
Method	mixed model for repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	0.017
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.191
upper limit	0.225
Variability estimate	Standard error of the mean
Dispersion value	0.106

Notes:

[28] - not adjusted for multiplicity

Secondary: Participants With Treatment-Emergent Adverse Events (TEAEs)

End point title	Participants With Treatment-Emergent Adverse Events (TEAEs)
End point description:	
<p>Adverse events (AEs) summarized in this table are those that began or worsened after treatment with study drug (treatment-emergent AEs). An adverse event was defined in the protocol as any untoward medical occurrence that develops or worsens in severity during the conduct of a clinical study and does not necessarily have a causal relationship to the study drug. Severity was rated by the investigator on a scale of mild, moderate and severe, with severe= an AE which prevents normal daily activities. Relation of AE to treatment was determined by the investigator.</p> <p>Serious AEs include death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, a congenital anomaly or birth defect, OR an important medical event that jeopardized the patient and required medical intervention to prevent the previously listed serious outcomes.</p>	
End point type	Secondary
End point timeframe:	
Early Start: Day 1 up to 6.5 years	
Delayed Start - Placebo: Day 1 up to Month 12	
Delayed Start - GA: Month 13 up to 6.5 years	

End point values	Entire Study: Early Start: GA 40 mg / GA 40 mg	OL Period - Delayed Start: GA 40 mg	PC Period- Delayed Start: Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	943 ^[29]	419 ^[30]	461 ^[31]	
Units: participants				
Severity of TEAEs: Mild	698	283	247	
Severity of TEAEs: Moderate	441	168	101	
Severity of TEAEs: Severe	95	24	16	
Treatment-related TEAEs	501	189	73	
Serious TEAEs	117	36	21	
Deaths	3	1	1	
TEAEs leading to treatment discontinuation	63	28	6	

Notes:

[29] - Safety

[30] - Safety

[31] - Safety

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Delayed Start (Placebo): Day 1 to Month 12

Delayed Start (GA 40 mg): Month 13 up to 6.5 years

Early Start: (GA 40 mg/ GA 40 mg) Day 1 up to 6.5 years

Adverse event reporting additional description:

Death details:

Delayed Start (Placebo): cardiopulmonary failure

Delayed Start (GA 40 mg): caused by subarachnoid hemorrhage and brain edema 1027 days after the first dose of GA.

Early Start: Three deaths due to acute cardiac failure, cardio-respiratory arrest, and cardiac arrest occurring 488, 1283 and 1682 days after first dose of GA

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	Delayed Start: Placebo
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Reporting group description:

Participants were administered placebo subcutaneous injections three times a week from Day 1 to Month 12 during the double-blind Placebo-Controlled Period.

Reporting group title	Delayed Start: GA 40 mg
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Reporting group description:

After completing the double-blind Placebo-Controlled Period, participants had the option of continuing in the study on glatiramer acetate (GA) 40 mg/ml by subcutaneous injection three times a week until the study ended.

This 'Delayed Start' treatment started at Month 13 and continued until the study ended (up to about 6.5 years).

Reporting group title	Early Start: GA 40 mg / GA 40 mg
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Reporting group description:

Participants were administered glatiramer acetate (GA) 40 mg/mL by subcutaneous injection three times a week for 12 months during the double-blind Placebo-Controlled Period, and then continued that treatment in the Open-label Period from Month 13 up to Year 6.5 until the study ended.

Serious adverse events	Delayed Start: Placebo	Delayed Start: GA 40 mg	Early Start: GA 40 mg / GA 40 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 461 (4.56%)	36 / 419 (8.59%)	117 / 943 (12.41%)
number of deaths (all causes)	1	1	3
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Thyroid cancer			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Seminoma			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cell carcinoma			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intraductal papilloma of breast			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast neoplasm			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaplastic astrocytoma			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal carcinoma			
subjects affected / exposed	1 / 461 (0.22%)	0 / 419 (0.00%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Follicular thyroid cancer			
subjects affected / exposed	1 / 461 (0.22%)	0 / 419 (0.00%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leiomyoma			

subjects affected / exposed	0 / 461 (0.00%)	1 / 419 (0.24%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	0 / 461 (0.00%)	1 / 419 (0.24%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Astrocytoma			
subjects affected / exposed	0 / 461 (0.00%)	1 / 419 (0.24%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	0 / 461 (0.00%)	2 / 419 (0.48%)	4 / 943 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Thrombophlebitis superficial			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral venous disease			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic dissection			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 461 (0.00%)	1 / 419 (0.24%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			

subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	2 / 943 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Inguinal hernia repair			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hysterectomy			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast conserving surgery			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureteric calculus removal			
subjects affected / exposed	1 / 461 (0.22%)	0 / 419 (0.00%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillectomy			
subjects affected / exposed	1 / 461 (0.22%)	0 / 419 (0.00%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toe amputation			
subjects affected / exposed	1 / 461 (0.22%)	0 / 419 (0.00%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervix operation			
subjects affected / exposed	1 / 461 (0.22%)	0 / 419 (0.00%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip arthroplasty			

subjects affected / exposed	0 / 461 (0.00%)	2 / 419 (0.48%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroidectomy			
subjects affected / exposed	0 / 461 (0.00%)	1 / 419 (0.24%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal operation			
subjects affected / exposed	0 / 461 (0.00%)	1 / 419 (0.24%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrectomy			
subjects affected / exposed	0 / 461 (0.00%)	1 / 419 (0.24%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mammoplasty			
subjects affected / exposed	0 / 461 (0.00%)	1 / 419 (0.24%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract operation			
subjects affected / exposed	0 / 461 (0.00%)	1 / 419 (0.24%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicectomy			
subjects affected / exposed	0 / 461 (0.00%)	1 / 419 (0.24%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion threatened			
subjects affected / exposed	1 / 461 (0.22%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abortion incomplete			

subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abortion spontaneous			
subjects affected / exposed	1 / 461 (0.22%)	1 / 419 (0.24%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immediate post-injection reaction			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Feeling hot			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema			
subjects affected / exposed	1 / 461 (0.22%)	0 / 419 (0.00%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chills			
subjects affected / exposed	0 / 461 (0.00%)	1 / 419 (0.24%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injection site swelling			
subjects affected / exposed	0 / 461 (0.00%)	1 / 419 (0.24%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injection site erythema			

subjects affected / exposed	0 / 461 (0.00%)	1 / 419 (0.24%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	0 / 461 (0.00%)	1 / 419 (0.24%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 461 (0.00%)	1 / 419 (0.24%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaphylactic reaction			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug hypersensitivity			
subjects affected / exposed	0 / 461 (0.00%)	2 / 419 (0.48%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Metrorrhagia			
subjects affected / exposed	1 / 461 (0.22%)	0 / 419 (0.00%)	2 / 943 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine cervical erosion			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Ovarian cyst			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oligomenorrhoea			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fibrocystic breast disease			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial hyperplasia			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical dysplasia			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenomyosis			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast disorder			
subjects affected / exposed	1 / 461 (0.22%)	0 / 419 (0.00%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine polyp			

subjects affected / exposed	0 / 461 (0.00%)	1 / 419 (0.24%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngeal oedema			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory arrest			
subjects affected / exposed	1 / 461 (0.22%)	0 / 419 (0.00%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 461 (0.22%)	0 / 419 (0.00%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 461 (0.00%)	2 / 419 (0.48%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infiltration			
subjects affected / exposed	0 / 461 (0.00%)	1 / 419 (0.24%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Anxiety			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bipolar I disorder			
subjects affected / exposed	0 / 461 (0.00%)	2 / 419 (0.48%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 461 (0.00%)	1 / 419 (0.24%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Weight decreased			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood pressure increased			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheterisation cardiac			
subjects affected / exposed	1 / 461 (0.22%)	0 / 419 (0.00%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Body temperature increased			
subjects affected / exposed	0 / 461 (0.00%)	1 / 419 (0.24%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Thermal burn			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Meniscus injury			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon injury			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Face injury			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Craniocerebral injury			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clavicle fracture			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Burns second degree			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laceration			
subjects affected / exposed	1 / 461 (0.22%)	0 / 419 (0.00%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple injuries			

subjects affected / exposed	1 / 461 (0.22%)	0 / 419 (0.00%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fractured skull depressed			
subjects affected / exposed	1 / 461 (0.22%)	0 / 419 (0.00%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot fracture			
subjects affected / exposed	1 / 461 (0.22%)	0 / 419 (0.00%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Contusion			
subjects affected / exposed	1 / 461 (0.22%)	0 / 419 (0.00%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain contusion			
subjects affected / exposed	1 / 461 (0.22%)	0 / 419 (0.00%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	1 / 461 (0.22%)	0 / 419 (0.00%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	0 / 461 (0.00%)	1 / 419 (0.24%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	0 / 461 (0.00%)	1 / 419 (0.24%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Forearm fracture			

subjects affected / exposed	0 / 461 (0.00%)	1 / 419 (0.24%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skull fracture			
subjects affected / exposed	0 / 461 (0.00%)	1 / 419 (0.24%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 461 (0.00%)	1 / 419 (0.24%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extradural haematoma			
subjects affected / exposed	0 / 461 (0.00%)	1 / 419 (0.24%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	0 / 461 (0.00%)	1 / 419 (0.24%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	2 / 943 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle fracture			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	2 / 943 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Congenital hydronephrosis			
subjects affected / exposed	0 / 461 (0.00%)	1 / 419 (0.24%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			

Cardiac arrest			
subjects affected / exposed	1 / 461 (0.22%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac failure acute			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardio-respiratory arrest			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Tachycardia			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Palpitations			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic cardiomyopathy			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			

subjects affected / exposed	1 / 461 (0.22%)	0 / 419 (0.00%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiopulmonary failure			
subjects affected / exposed	1 / 461 (0.22%)	0 / 419 (0.00%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 461 (0.22%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Trigeminal neuralgia			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Status epilepticus			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Optic neuritis			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar radiculopathy			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			

subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Idiopathic generalised epilepsy			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carpal tunnel syndrome			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	1 / 461 (0.22%)	0 / 419 (0.00%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	1 / 461 (0.22%)	0 / 419 (0.00%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Apallic syndrome			
subjects affected / exposed	1 / 461 (0.22%)	0 / 419 (0.00%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 461 (0.00%)	1 / 419 (0.24%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple sclerosis relapse			
subjects affected / exposed	1 / 461 (0.22%)	2 / 419 (0.48%)	5 / 943 (0.53%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain oedema			

subjects affected / exposed	0 / 461 (0.00%)	1 / 419 (0.24%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	3 / 943 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	3 / 943 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	2 / 943 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbosacral radiculopathy			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	2 / 943 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iron deficiency anaemia			
subjects affected / exposed	0 / 461 (0.00%)	1 / 419 (0.24%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Hypoacusis			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertigo positional			

subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Macular oedema			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Glaucoma			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iridocyclitis			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract			
subjects affected / exposed	0 / 461 (0.00%)	1 / 419 (0.24%)	2 / 943 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Pancreatitis chronic			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids thrombosed			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal hernia			

subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroduodenitis			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Swollen tongue			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 461 (0.22%)	0 / 419 (0.00%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal fistula			

subjects affected / exposed	0 / 461 (0.00%)	1 / 419 (0.24%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proctitis			
subjects affected / exposed	0 / 461 (0.00%)	1 / 419 (0.24%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 461 (0.00%)	1 / 419 (0.24%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic gastritis			
subjects affected / exposed	0 / 461 (0.00%)	1 / 419 (0.24%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 461 (0.00%)	1 / 419 (0.24%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 461 (0.00%)	1 / 419 (0.24%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	2 / 943 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatitis toxic			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice cholestatic			

subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis chronic			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder polyp			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	1 / 461 (0.22%)	1 / 419 (0.24%)	3 / 943 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug-induced liver injury			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	2 / 943 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psoriasis			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pruritus			

subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Panniculitis			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erythema			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkeratosis			
subjects affected / exposed	0 / 461 (0.00%)	1 / 419 (0.24%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urticaria			
subjects affected / exposed	1 / 461 (0.22%)	1 / 419 (0.24%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angioedema			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	2 / 943 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Urinary incontinence			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stress urinary incontinence			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Perinephritis			

subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureterolithiasis			
subjects affected / exposed	1 / 461 (0.22%)	0 / 419 (0.00%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	1 / 461 (0.22%)	0 / 419 (0.00%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal colic			
subjects affected / exposed	1 / 461 (0.22%)	0 / 419 (0.00%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	1 / 461 (0.22%)	0 / 419 (0.00%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anuria			
subjects affected / exposed	1 / 461 (0.22%)	0 / 419 (0.00%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cyst			
subjects affected / exposed	0 / 461 (0.00%)	1 / 419 (0.24%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 461 (0.00%)	1 / 419 (0.24%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Osteoarthritis			

subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Synovitis			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spondylolisthesis			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spondylitis			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myositis			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc disorder			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot deformity			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Exostosis			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chondropathy			

subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis			
subjects affected / exposed	0 / 461 (0.00%)	1 / 419 (0.24%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 461 (0.00%)	1 / 419 (0.24%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Latent tuberculosis			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ophthalmic herpes zoster			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal sepsis			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			

subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis chronic			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nail infection			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injection site abscess			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis B			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis rotavirus			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder empyema			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Burn infection			

subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone tuberculosis			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	2 / 461 (0.43%)	0 / 419 (0.00%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	1 / 461 (0.22%)	0 / 419 (0.00%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vestibular neuronitis			
subjects affected / exposed	1 / 461 (0.22%)	0 / 419 (0.00%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 461 (0.00%)	2 / 419 (0.48%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 461 (0.00%)	1 / 419 (0.24%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis perforated			
subjects affected / exposed	0 / 461 (0.00%)	1 / 419 (0.24%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salpingitis			

subjects affected / exposed	0 / 461 (0.00%)	1 / 419 (0.24%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Helicobacter infection			
subjects affected / exposed	0 / 461 (0.00%)	1 / 419 (0.24%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendiceal abscess			
subjects affected / exposed	0 / 461 (0.00%)	1 / 419 (0.24%)	0 / 943 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	4 / 943 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 461 (0.00%)	1 / 419 (0.24%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	0 / 461 (0.00%)	1 / 419 (0.24%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	3 / 943 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	2 / 943 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			

subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	2 / 943 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	2 / 943 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrolyte imbalance			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus			
subjects affected / exposed	0 / 461 (0.00%)	0 / 419 (0.00%)	1 / 943 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Delayed Start: Placebo	Delayed Start: GA 40 mg	Early Start: GA 40 mg / GA 40 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	167 / 461 (36.23%)	238 / 419 (56.80%)	609 / 943 (64.58%)
Nervous system disorders			
Headache			
subjects affected / exposed	55 / 461 (11.93%)	39 / 419 (9.31%)	132 / 943 (14.00%)
occurrences (all)	71	83	316

Multiple sclerosis relapse subjects affected / exposed occurrences (all)	7 / 461 (1.52%) 9	10 / 419 (2.39%) 12	48 / 943 (5.09%) 63
General disorders and administration site conditions			
Injection site erythema subjects affected / exposed occurrences (all)	8 / 461 (1.74%) 10	107 / 419 (25.54%) 122	243 / 943 (25.77%) 391
Injection site pain subjects affected / exposed occurrences (all)	10 / 461 (2.17%) 10	55 / 419 (13.13%) 61	115 / 943 (12.20%) 138
Injection site pruritus subjects affected / exposed occurrences (all)	2 / 461 (0.43%) 2	23 / 419 (5.49%) 24	68 / 943 (7.21%) 95
Injection site swelling subjects affected / exposed occurrences (all)	3 / 461 (0.65%) 3	23 / 419 (5.49%) 23	50 / 943 (5.30%) 95
Musculoskeletal and connective tissue disorders			
Back pain subjects affected / exposed occurrences (all)	20 / 461 (4.34%) 26	33 / 419 (7.88%) 45	98 / 943 (10.39%) 150
Infections and infestations			
Nasopharyngitis subjects affected / exposed occurrences (all)	39 / 461 (8.46%) 47	56 / 419 (13.37%) 98	167 / 943 (17.71%) 346
Urinary tract infection subjects affected / exposed occurrences (all)	22 / 461 (4.77%) 24	36 / 419 (8.59%) 50	103 / 943 (10.92%) 165
Upper respiratory tract infection subjects affected / exposed occurrences (all)	25 / 461 (5.42%) 30	32 / 419 (7.64%) 54	98 / 943 (10.39%) 158
Influenza subjects affected / exposed occurrences (all)	17 / 461 (3.69%) 22	25 / 419 (5.97%) 33	67 / 943 (7.10%) 103
Bronchitis subjects affected / exposed occurrences (all)	7 / 461 (1.52%) 9	20 / 419 (4.77%) 25	50 / 943 (5.30%) 65

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 July 2010	<ul style="list-style-type: none">- To clarify the definition of MRI secondary and add exploratory endpoints* (derived from the same outcome measures already defined in the protocol, namely new T2 and new hypointense T1 lesions). <p>*Note: This was a typographical error made in the protocol amendment. Wording in the amendment should actually read: "To clarify the definition of MRI secondary and exploratory endpoints, and to add exploratory endpoints."</p> <ul style="list-style-type: none">- To limit the anti-GA antibody ancillary study to a subset of approximately 400 subjects in total- To remove 4-amino-pyridine from the disallowed medications list- To add an Exclusion Criterion No. 16 to exclude subjects who underwent endovascular treatment for chronic cerebrospinal venous insufficiency (CCSV)- To reduce the pharmacogenetics (PGx) samples to 1 sample instead of 2 during the study- To correct typographical errors, which were discovered following submission of the protocol.
01 January 2012	<ul style="list-style-type: none">- To add new covariates to the list of pre-defined covariates of the primary endpoint and several exploratory endpoints- To redefine the timeframe for the baseline visit activities in the OL extension phase of the study- To redefine activities at visits 4 and 5 (months 9 and 12) of PC phase of the study- To define the study periods in the OL extension phase for neurological/medical assessment activities- To define the Study Neurologist/Physician's responsibilities- To correct typographical errors that occurred during the previous amendment- To change the title of Clinical Leader to Clinical Project Physician and the name of the responsible person
01 January 2013	<ul style="list-style-type: none">- Addition of MRI at month 36 in the OL extension phase- Correction of typographical errors found in the definition of some MRI exploratory endpoints

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported