Clinical trial results:
A double-blind, randomized, multicenter, placebo-controlled, parallel-group study comparing the efficacy and safety of 0.5 mg fingolimod administered orally once daily versus placebo in patients with primary progressive multiple sclerosis (PPMS) with an open-label, single-arm extension study to the double-blind, randomized, multicenter, placebo-controlled, parallel-group study comparing the efficacy and safety of 0.5 mg FTY720 administered orally once daily versus placebo in patients with primary progressive multiple sclerosis

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.nov for complete trial results.

Summary

EudraCT number	2007-002627-32
Trial protocol	CZ GB FI SE ES FR IT DE NL BE HU DK
Global end of trial date	22 June 2015

Results information

Result version number	v1 (current)
This version publication date	19 July 2018
First version publication date	19 July 2018

Trial information

Trial identification

Sponsor protocol code	CFTY720D2306/CFTY720D2306E1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00731692
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, trialandresults.registries@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111 x, trialandresults.registries@novartis.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 June 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 June 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the effect of fingolimod 0.5 mg relative to placebo on delaying the time to sustained disability progression and To assess the long-term safety and tolerability of fingolimod 0.5 mg/day in patients with primary progressive multiple sclerosis (PPMS)

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 July 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 77
Country: Number of subjects enrolled	Spain: 102
Country: Number of subjects enrolled	United States: 120
Country: Number of subjects enrolled	Belgium: 21
Country: Number of subjects enrolled	Canada: 112
Country: Number of subjects enrolled	Czech Republic: 39
Country: Number of subjects enrolled	Finland: 14
Country: Number of subjects enrolled	France: 94
Country: Number of subjects enrolled	Italy: 108
Country: Number of subjects enrolled	Netherlands: 60

Country: Number of subjects enrolled	Sweden: 17
Country: Number of subjects enrolled	Switzerland: 30
Country: Number of subjects enrolled	Turkey: 23
Country: Number of subjects enrolled	United Kingdom: 64
Country: Number of subjects enrolled	Australia: 38
Country: Number of subjects enrolled	Hungary: 28
Country: Number of subjects enrolled	Denmark: 4
Country: Number of subjects enrolled	Poland: 19
Worldwide total number of subjects	970
EEA total number of subjects	647

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)	957
From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were randomized to receive fingolimod or placebo. Patients initially randomized to fingolimod 1.25 mg/day placebo were switched in a blinded manner to fingolimod 0.5 mg/day or continued on placebo after amendment. Patients were randomized to either fingolimod 0.5 mg/day or placebo.

Pre-assignment

Screening details:

Prior to amendment, 147 patients received 1.25mg of FTY720, post amendment, patients switched to 0.5mg FTY720 and their data was presented under the 0.5mg dose.

Period 1

Period 1 title	Core study
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	FTY720 1.25 mg

Arm description:

Cohort 1: fingolimod 1.25 group consists of patients who were initially randomized to fingolimod 1.25 mg and switched to fingolimod 0.5 mg after amendment

Arm type	Experimental
Investigational medicinal product name	Fingolimod
Investigational medicinal product code	FTY720
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Fingolimod 1.25 mg oral capsules once daily

Arm title	FTY720 0.5 mg

Arm description:

Cohort 2: The 0.5 mg group consists of patients who were directly randomized to fingolimod 0.5 mg (i.e. AFTER the amendment)

Arm type	Experimental
Investigational medicinal product name	Fingolimod
Investigational medicinal product code	FTY720
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Fingolimod 0.5 mg oral capsules once daily

Arm title	Placebo (all)-FTY 0.5

Arm description:

Cohort 1 and 2: Patients who started on placebo continued on placebo after re-randomization

Arm type	Placebo

Investigational medicinal product name	Fingolimod
Investigational medicinal product code	FTY720
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Matching placebo given orally once daily

Number of subjects in period 1	FTY720 1.25 mg	FTY720 0.5 mg	Placebo (all)-FTY 0.5
Started	147	336	487
Safety Set (SAF)	0 [1]	336	487
Full analysis Set (FAS)	0 [2]	336	487
Pharmacokinetic Analysis Set	102	249	0 [3]
Completed	79	220	317
Not completed	68	116	170
Adverse event, serious fatal	2	1	2
Physician decision	1	-	2
Consent withdrawn by subject	12	32	46
Administrative	2	2	6
Adverse event, non-fatal	25	28	29
Abnormal Test Procedure Result	4	3	5
Abnormal lab values	6	19	5
Lost to follow-up	1	3	3
Lack of efficacy	11	23	64
Protocol deviation	4	5	8

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Number verified and correct

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Number verified and correct

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Number verified and correct

Period 2

Period 2 title	Extension phase
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms	
Are arms mutually exclusive?	Yes
Arm title	FTY720 1.25 mg

Arm description:

Cohort 1: fingolimod 1.25 group consists of patients who were initially randomized to fingolimod 1.25 mg and switched to fingolimod 0.5 mg after amendment

Arm type	Experimental
Investigational medicinal product name	Fingolimod
Investigational medicinal product code	FTY720
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Fingolimod 1.25 mg oral capsules once daily

Arm title	FTY720 0.5 mg

Arm description:

Cohort 2: The 0.5 mg group consists of patients who were directly randomized to fingolimod 0.5 mg (i.e. AFTER the amendment)

Arm type	Experimental
Investigational medicinal product name	Fingolimod
Investigational medicinal product code	FTY720
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

FTY720 0.5 mg oral capsule, given once daily

Arm title	Placebo (all)-FTY 0.5

Arm description:

Cohort 1 and 2: Patients who started on placebo continued on placebo after re-randomization

Arm type	Experimental
Investigational medicinal product name	Fingolimod
Investigational medicinal product code	FTY720
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Matching placebo given orally once daily

Number of subjects in period 2[4]	FTY720 1.25 mg	FTY720 0.5 mg	Placebo (all)-FTY 0.5
Started	74	196	301
Completed	0	0	0
Not completed	74	196	301
Consent withdrawn by subject	4	5	3
Abnormal test procedure	-	-	1
Adverse event, non-fatal	1	1	15

administrative problems; Terminated # patients	69	189	277
Abnormal lab values	-	-	1
Lost to follow-up	-	1	4

Notes:

[4] - 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: Number verified and correct

Baseline characteristics

Reporting groups	
Reporting group title	FTY720 1.25 mg
Reporting group description:	
Cohort 1: fingolimod 1.25 group consists of patients who were initially randomized to fingolimod 1.25 mg and switched to fingolimod 0.5 mg after amendment	
Reporting group title	FTY720 0.5 mg
Reporting group description:	
Cohort 2: The 0.5 mg group consists of patients who were directly randomized to fingolimod 0.5 mg (i.e. AFTER the amendment)	
Reporting group title	Placebo (all)-FTY 0.5
Reporting group description:	
Cohort 1 and 2: Patients who started on placebo continued on placebo after re-randomization	

Reporting group values	FTY720 1.25 mg	FTY720 0.5 mg	Placebo (all)-FTY 0.5
Number of subjects	147	336	487
Age, Customized Units: Particpants			
<=30	3	6	4
31 to 40	22	60	90
41 to 50	68	127	194
>50	54	143	199
Age Continuous Units: years			
arithmetic mean	47.8	48.5	48.5
standard deviation	± 8.47	± 8.59	± 8.31
Gender, Male/Female Units: Participants			
Female	71	163	235
Male	76	173	252

Reporting group values	Total		
Number of subjects	970		
Age, Customized Units: Particpants			
<=30	13		
31 to 40	172		
41 to 50	389		
>50	396		
Age Continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender, Male/Female Units: Participants			
Female	469		
Male	501		

Subject analysis sets	
Subject analysis set title	Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Cohort 1 and 2: Patients who started on placebo continued on placebo after re-randomization	
Subject analysis set title	Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Cohort 1 and 2: Patients who started on placebo continued on placebo after re-randomization	
Subject analysis set title	Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Cohort 1 and 2: Patients who started on placebo continued on placebo after re-randomization	
Subject analysis set title	Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Cohort 1 and 2: Patients who started on placebo continued on placebo after re-randomization	
Subject analysis set title	Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Cohort 1 and 2: Patients who started on placebo continued on placebo after re-randomization	
Subject analysis set title	FTY720 1.25mg to 0.5 mg
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
fingolimod 1.25mg/0.5 mg group consists of patients who were initially randomized to fingolimod 1.25 mg and switched to fingolimod 0.5 mg	
Subject analysis set title	Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Cohort 1 and 2: Patients who started on placebo continued on placebo after re-randomization	

Reporting group values	Placebo	Placebo	Placebo
Number of subjects	487	421	133
Age, Customized Units: Particpants			
<=30	4		
31 to 40	90		
41 to 50	194		
>50	199		
Age Continuous Units: years			
arithmetic mean	48.5		
standard deviation	± 8.31	±	±
Gender, Male/Female Units: Participants			
Female	235		
Male	252		

Reporting group values	Placebo	Placebo	FTY720 1.25mg to 0.5 mg
Number of subjects	320	326	102

Age, Customized Units: Particpants			
<=30 31 to 40 41 to 50 >50			
Age Continuous Units: years arithmetic mean standard deviation	±	±	±
Gender, Male/Female Units: Participants			
Female Male			

Reporting group values	Placebo		
Number of subjects	279		
Age, Customized Units: Particpants			
<=30 31 to 40 41 to 50 >50			
Age Continuous Units: years arithmetic mean standard deviation	±		
Gender, Male/Female Units: Participants			
Female Male			

End points

End points reporting groups

Reporting group title	FTY720 1.25 mg
Reporting group description:	
Cohort 1: fingolimod 1.25 group consists of patients who were initially randomized to fingolimod 1.25 mg and switched to fingolimod 0.5 mg after amendment	
Reporting group title	FTY720 0.5 mg
Reporting group description:	
Cohort 2: The 0.5 mg group consists of patients who were directly randomized to fingolimod 0.5 mg (i.e. AFTER the amendment)	
Reporting group title	Placebo (all)-FTY 0.5
Reporting group description:	
Cohort 1 and 2: Patients who started on placebo continued on placebo after re-randomization	
Reporting group title	FTY720 1.25 mg
Reporting group description:	
Cohort 1: fingolimod 1.25 group consists of patients who were initially randomized to fingolimod 1.25 mg and switched to fingolimod 0.5 mg after amendment	
Reporting group title	FTY720 0.5 mg
Reporting group description:	
Cohort 2: The 0.5 mg group consists of patients who were directly randomized to fingolimod 0.5 mg (i.e. AFTER the amendment)	
Reporting group title	Placebo (all)-FTY 0.5
Reporting group description:	
Cohort 1 and 2: Patients who started on placebo continued on placebo after re-randomization	
Subject analysis set title	Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Cohort 1 and 2: Patients who started on placebo continued on placebo after re-randomization	
Subject analysis set title	Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Cohort 1 and 2: Patients who started on placebo continued on placebo after re-randomization	
Subject analysis set title	Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Cohort 1 and 2: Patients who started on placebo continued on placebo after re-randomization	
Subject analysis set title	Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Cohort 1 and 2: Patients who started on placebo continued on placebo after re-randomization	
Subject analysis set title	Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Cohort 1 and 2: Patients who started on placebo continued on placebo after re-randomization	
Subject analysis set title	FTY720 1.25mg to 0.5 mg
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
fingolimod 1.25mg/0.5 mg group consists of patients who were initially randomized to fingolimod 1.25 mg and switched to fingolimod 0.5 mg	
Subject analysis set title	Placebo
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Cohort 1 and 2: Patients who started on placebo continued on placebo after re-randomization

Primary: Kaplan-Meier estimate of the risk of 3-month confirmed disability progression based on composite endpoint

End point title	Kaplan-Meier estimate of the risk of 3-month confirmed disability progression based on composite endpoint[1]

End point description:

3-month sustained increase from Baseline in EDSS (at least 1 point increase from Baseline for patients with a Baseline value of 5 or less or at least 0.5 point increase from Baseline for patients with a Baseline value of 5.5 or more) or 3-month sustained increase of at least 20% from BL in the time taken to complete the timed 25-foot walk test (25' TWT); or 3-month sustained increase of at least 20% from BL in the time taken to complete the 9-HPT. The 25' TWT is a quantitative measure of lower extremity function. The EDSS is a scale assessing neurologic impairment, including a series of scores in each of 8 functional systems: Visual, Brain Stem, Pyramidal, Cerebellar, Sensory, Bowel and Bladder, Cerebral and Other functions. The score ranges from 0 (normal) to 10 (death due to MS)). The 9-hole peg test (9-HPT) is a quantitative measure of upper extremity (arm and hand) function.

End point type	Primary

End point timeframe:

up to 36 months after the last patient was randomized

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was completed for secondary outcome measures

End point values	FTY720 0.5 mg	Placebo		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	336	487		
Units: Percentage of Participants				
number (confidence interval 95%)	77.2 (71.87 to 82.51)	80.3 (73.31 to 87.25)		

Statistical analyses

Statistical analysis title	Risk of 3-month confirmed disability progression
Comparison groups	FTY720 0.5 mg v Placebo
Number of subjects included in analysis	823
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.544
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.12
Variability estimate	Standard error of the mean

Secondary: Kaplan-Meier estimate of the risk of 3- month confirmed disability progression based on Expanded Disability Status Scale (EDSS)

End point title	Kaplan-Meier estimate of the risk of 3- month confirmed disability progression based on Expanded Disability Status Scale (EDSS)[2]

End point description:

The Expanded Disability Status Scale (EDSS) is a scale for assessing neurologic impairment in MS (Kurtzke 1983) and includes a series of scores in each of 8 functional systems and the EDSS steps (ranging from 0 (normal) to 10 (death due to MS)). The functional systems are Visual, Brain Stem, Pyramidal, Cerebellar, Sensory, Bowel and Bladder, Cerebral and Other functions. Fatigue is not included in the Cerebral score of the EDSS. The score ranges from 0 (normal) to 10 (death due to MS)

End point type	Secondary

End point timeframe:

up to 36 months after the last patient was randomized

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was completed for secondary outcome measures

End point values	FTY720 0.5 mg	Placebo		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	336	487		
Units: Percentage of Participants				
number (confidence interval 95%)	54.3 (47.16 to 61.45)	58.7 (53.3 to 64.18)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from baseline in brain volume at Month 36

End point title	Percent change from baseline in brain volume at Month 36[3]

End point description:

The percent change from Baseline in brain volume was analyzed using a random coefficients model. The model included: 1) fixed effects: treatment and region and 2) continuous covariates: time, number of Gd enhancing lesions at Baseline, Baseline T2 volume, and normalized brain volume at Baseline. Time as a continuous covariate allowed for the estimation of different slopes and intercepts among treatment groups.

End point type	Secondary

End point timeframe:

Baseline to month 36

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was completed for secondary outcome measures

End point values	FTY720 0.5 mg	Placebo		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	293	421		
Units: Percent Change				
least squares mean (confidence interval 95%)	-1.49 (-1.64 to -1.35)	-1.53 (-1.65 to -1.41)		

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan Meier Estimate -Percentage of participants with 3- month confirmed disability progression based on 9-HPT.

End point title	Kaplan Meier Estimate -Percentage of participants with 3-month confirmed disability progression based on 9-HPT.[4]

End point description:

The 9-HPT is a quantitative measure of upper extremity (arm and hand) function designed and validated for evaluation of MS patients. N= Total number of patients included in the analysis

End point type	Secondary

End point timeframe:

up to 36 months after the last patient was randomized

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was completed for secondary outcome measures

End point values	FTY720 0.5 mg	Placebo		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	147	133		
Units: Percentge of Participants				
number (not applicable)	25	24.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan Meier Estimate -Percentage of participants with 3- month confirmed disability progression based on 25' TWT.

End point title	Kaplan Meier Estimate -Percentage of participants with 3-month confirmed disability progression based on 25' TWT.[5]

End point description:

The 25' TWT is a quantitative measure of lower extremity function designed and validated for evaluation of MS patients. N= Total number of patients included in the analysis

End point type	Secondary

End point timeframe:

up to 36 months after the last patient was randomized

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was completed for secondary outcome measures

End point values	FTY720 0.5 mg	Placebo		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	147	133		
Units: Percentage of Participants				
number (not applicable)	54.8	56.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of new/enlarging T2 lesions per year measured from baseline to Month 36

End point title	Number of new/enlarging T2 lesions per year measured from baseline to Month 36[6]

End point description:

Inflammatory disease, as measured by number of new or newly-enlarging T2 lesions, was assessed by Magnetic resonance Imaging (MRI) scanning of the brain and full spinal cord. N= Total number of patients included in the analysis

End point type	Secondary

End point timeframe:

Baseline to 36 months

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was completed for secondary outcome measures

End point values	FTY720 0.5 mg	Placebo		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	298	421		
Units: T2 Lesions per year				
least squares mean (confidence interval 95%)	0.13 (0.1 to 0.18)	0.5 (0.4 to 0.61)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Gd-enhancing lesions at month 36

End point title	Number of Gd-enhancing lesions at month 36[7]

End point description:

Inflammatory disease, as measured by number of T1 Gd-enhancing lesions, was assessed by MRI scanning of the brain and full spinal cord. N= Total number of patients included in the analysis

End point type	Secondary

End point timeframe:

Baseline to 36 months

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was completed for secondary outcome measures

End point values	FTY720 0.5 mg	Placebo		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	223	320		
Units: Gd-enhanced lesions per patient per scan				
least squares mean (confidence interval 95%)	0.05 (0.02 to 0.09)	0.21 (0.15 to 0.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in total T2 lesion volume from baseline to Month 36

End point title	Percent change in total T2 lesion volume from baseline to Month 36[8]

End point description:

Inflammatory disease as measured by percent change in total T2 lesion volume (mm3) was assessed by MRI. N= Total number of patients included in the analysis

End point type	Secondary

End point timeframe:

Baseline to month 36

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was completed for secondary outcome measures

End point values	FTY720 0.5 mg	Placebo		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	224	326		
Units: Percent Change				
arithmetic mean (standard deviation)	-9.2 (± 30.55)	8.9 (± 44.13)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the patient reported indices in multiple sclerosis (PRIMUS-QoL score)

End point title	Change from baseline in the patient reported indices in multiple sclerosis (PRIMUS-QoL score)[9]

End point description:

The quality of life scale contains 22 items. Each item will be given a score of 1 or 0. A score of 1 (or 0) indicates the presence (or absence) of the symptom or adverse quality of life. All 22 item scores will be summed to obtain a total score ranging from 0 (good) to 22 (poor), which is the PRIMUS QoL scale

score

End point type	Secondary

End point timeframe:

Baseline, 36 months

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was completed for secondary outcome measures

End point values	FTY720 1.25 mg	FTY720 0.5 mg	Placebo	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	147	336	487	
Units: Score on a scale				
arithmetic mean (standard deviation)				
Baseline (n=100,246,352)	7.5349 (± 4.77306)	7.7197 (± 5.2922)	7.1693 (± 4.89106)	
Month 36 (n=66,150,230)	0.2424 (± 4.18444)	0.5921 (± 4.77704)	0.9597 (± 4.38578)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in PRIMUS-Activities

End point title	Change from baseline in PRIMUS-Activities[10]

End point description:

The activities subscale of PRIMUS contains 15 items and each item is given a score of 0 (able to do on own without difficulties), 1 (able to do on own with difficulties), or 2 (unable to do on own). All 15 items were summed to obtain a total score ranging from 0 (good) to 30 (poor).

End point type	Secondary

End point timeframe:

Baseline, 36 months

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was completed for secondary outcome measures

End point values	FTY720 1.25 mg	FTY720 0.5 mg	Placebo	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	147	336	487	
Units: Score on a scale				
arithmetic mean (standard deviation)				
Baseline (n=104,247,357)	9.3729 (± 5.74726)	10.1707 (± 5.96238)	10.0543 (± 6.25051)	
Month 36 (n=68,153,237)	3.5504 (± 7.05241)	2.6324 (± 6.22256)	2.883 (± 6.76499)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Unidimensional Fatigue Impact (U-FIS) score

End point title	Change from baseline in Unidimensional Fatigue Impact (U-FIS) score[11]

End point description:

Unidimensional Fatigue Impact Scale (U-FIS), contains 22 patient-reported items that assess the impact of fatigue on cognitive, physical, and psychosocial functioning. Responses formed a single unidimensional scale measuring fatigue impact. The U-FIS was calculated and analyzed according to the U-FIS scoring manual. The U-FIS scale contains 22 items with 5 possible outcomes for each item. Two response categories (about half the time and a lot of the time) were combined into 1 category to obtain 4 possible outcomes: 0 (never), 1 (a little of the time), 2 (about half the time/a lot of the time), and 3 (all the time). The 22 condensed item scores were summed to obtain a total score ranging from 0 (no fatigue) to 66 (severe fatigue impact).

End point type	Secondary

End point timeframe:

Baseline, 36 months

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was completed for secondary outcome measures

End point values	FTY720 1.25 mg	FTY720 0.5 mg	Placebo	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	147	336	487	
Units: Score on a scale				
arithmetic mean (standard deviation)				
Baseline (n=103,248,357)	24.1937 (± 12.66758)	25.7206 (± 13.63297)	23.8297 (± 13.02168)	
Month 36 (n=70,154,241)	1.3197 (± 12.44042)	2.8451 (± 14.04769)	3.1394 (± 12.20929)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in European Quality of Life – 5 dimensions (EQ-5D score)

End point title	Change from baseline in European Quality of Life – 5 dimensions (EQ-5D score)[12]

End point description:

EQ-5D: participant rated questionnaire to assess health-related quality of life in terms of a single utility score. Health State Profile component assesses level of current health for 5 domains: mobility, self care, usual activities, pain and discomfort, and anxiety and depression; 1 indicates better health state (no problems); 3 indicates worst health state (confined to bed). Scoring formula developed by EuroQoL Group assigns a utility value for each domain in the profile. Score is transformed and results in a total score range -0.594 to 1.000; higher score indicates a better health state.

End point type	Secondary

End point timeframe:

Baseline, 36 months

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was completed for secondary outcome measures

End point values	FTY720 1.25 mg	FTY720 0.5 mg	Placebo	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	147	336	487	
Units: Score on a scale				
arithmetic mean (standard deviation)				
Baseline (n=144,328,474)	0.6418 (± 0.1906)	0.6154 (± 0.21562)	0.6431 (± 0.18472)	
Month 36 (n=99,213,320)	-0.0332 (± 0.1942)	-0.0475 (± 0.26099)	-0.0539 (± 0.22383)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Multiple Sclerosis Walking Scale (MSWS-12 score)

End point title	Change from baseline in Multiple Sclerosis Walking Scale (MSWS-12 score)[13]

End point description:

The Multiple Sclerosis Walking Scaleis a patient reported measure of walking quality (Hobart et al 2003), consisting of 12 items asking patients to rate the impact of MS upon their walking ability. Responses were captured on a 3-point scale ranging from 1 (Not at all) to 3 (A lot) for items 1 to 3 and on a 5-point scale ranging from 1 (not limited) to 5 (extremely) for items 4 to 12. All 12 item scores were summed to obtain a total score ranging from 12 (good) to 54 (poor) which is the MSWS-12 scale score. The total score was transformed to a 0 to 100 scale score. The MSWS-12 scale score will be transformed to a 0-100 scale score before any summaries or statistical analyses are performed. The transformed score is obtained by subtracting 12 and divided by 42 and multiplying by 100 (i.e., transformed scale score = (raw scale score- 12)/42*100).

End point type	Secondary

End point timeframe:

Baseline, 36 months

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was completed for secondary outcome measures

End point values	FTY720 1.25 mg	FTY720 0.5 mg	Placebo	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	147	336	487	
Units: Score on a scale				
arithmetic mean (standard deviation)				
Baseline (n=115,278,397)	59.3892 (± 21.84532)	60.4606 (± 23.35639)	58.2921 (± 23.47897)	
Month 36 (n=75,182,261)	6.4444 (± 23.81568)	5.5616 (± 24.5903)	9.5899 (± 23.98316)	

Statistical analyses

No statistical analyses for this end point

Secondary: Blood concentrations of fingolimod and fingolimod-phosphate

End point title	Blood concentrations of fingolimod and fingolimod-

End point description:

Concentrations of fingolimod and fingolimod-phosphate in whole blood were determined by validated liquid chromatography methods with tandem mass spectrometry. The lower limits of quantification were 0.08 ng/ml for fingolimod and 0.1 ng/ml for fingolimod-phosphate. Venous blood samples were collected for the analysis.

End point type	Secondary

End point timeframe:

Month 3 up to 36 months

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was completed for secondary outcome measures

End point values	FTY720 1.25 mg	FTY720 0.5 mg	FTY720 1.25mg to 0.5	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	102	249	102	
Units: ng/ml				
arithmetic mean (standard deviation)				
Month 3 Fingolimod (n=64, 179)	6.04 (± 3.11)	2.58 (± 1.34)	999.99 (± 99.9)	
Month 12 Fingolimod (n=23, 161)	6.24 (± 2.21)	2.55 (± 1.37)	2.87 (± 1.7)	
Month 18 Fingolimod (n=71,155)	999.99 (± 99.9)	2.59 (± 1.44)	2.44 (± 1.15)	
Month 24 Fingolimod (n=67, 160)	999.99 (± 99.9)	2.64 (± 1.5)	2.41 (± 1.3)	
Month 30 Fingolimod (n=62, 158)	999.99 (± 99.9)	2.6 (± 1.33)	2.52 (± 1.28)	
Month 36 Fingolimod (n=55, 118)	999.99 (± 99.9)	2.63 (± 1.38)	2.44 (± 1.08)	
End of treatment Fingolimod (n=32, 115)	999.99 (± 99.9)	2.57 (± 1.51)	2.02 (± 1.1)	
Month 3 Fingolimod-Phosphate (n=64, 179)	3.2 (± 1.73)	1.4 (± 0.747)	999.99 (± 99.9)	
Month 12 Fingolimod-Phosphate (n=23, 161)	3.21 (± 1.16)	1.43 (± 0.805)	1.54 (± 0.871)	
Month 18 Fingolimod-Phosphate (n=71,155)	999.99 (± 99.9)	1.41 (± 0.758)	1.34 (± 0.63)	
Month 24 Fingolimod-Phosphate (n=67, 160)	999.99 (± 99.9)	1.44 (± 0.79)	1.35 (± 0.765)	
Month 30 Fingolimod-Phosphate (n=62, 158)	999.99 (± 99.9)	1.48 (± 0.759)	1.32 (± 0.676)	

Month 36 Fingolimod-Phosphate (n=55, 118)	999.99 (± 99.9)	1.51 (± 0.765)	1.32 (± 0.591)	
End of treatment Fingolimod-Phosphate (n=32, 115	999.99 (± 99.9)	1.5 (± 0.9)	1.19 (± 0.618)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in MSFC z-score and subscale scores from Baseline to Month 36

End point title	Change in MSFC z-score and subscale scores from Baseline to Month 36[15]

End point description:

The Multiple Sclerosis Functional Composite (MSFC) is a multidimensional clinical outcome measure that includes quantitative tests of leg function/ambulation (Timed 25-Foot Walk), arm function (9-Hole Peg Test), and cognitive function (Paced Auditory Serial Addition Test). The overall MSFC z-score as an average of the three standardized scores derived using baseline data pooled over each treatment arm as reference population. Higher scores reflect better neurological function and a positive change from Baseline indicates improvement.

End point type	Secondary

End point timeframe:

Baseline to Month 36

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was completed for secondary outcome measures

End point values	FTY720 0.5 mg	Placebo		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	193	279		
Units: Z-scores				
arithmetic mean (standard deviation)	-0.189 (± 0.698)	-0.212 (± 0.8468)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Core: FTY720 1.25 mg

Reporting group description:

Cohort 1: fingolimod 1.25 group consists of patients who were initially randomized to fingolimod 1.25 mg and switched to fingolimod 0.5 mg after amendment

Reporting group title	Core: FTY720 0.5 mg

Reporting group description:

Cohort 2: The 0.5 mg group consists of patients who were directly randomized to fingolimod 0.5 mg (i.e. AFTER the amendment)

Reporting group title	Core: Placebo

Reporting group description:

Cohort 1 and 2: Patients who started on placebo continued on placebo after re-randomization

Reporting group title	Extension: FTY1.25-0.5

Reporting group description:

Cohort 1: fingolimod 1.25 group consists of patients who were initially randomized to fingolimod 1.25 mg and switched to fingolimod 0.5 mg after amendment

Reporting group title	Extension: FTY0.5-0.5

Reporting group description:

Cohort 2: The 0.5 mg group consists of patients who were directly randomized to fingolimod 0.5 mg (i.e. AFTER the amendment)

Reporting group title	Extension: Placebo-FTY0.5

Reporting group description:

Cohort 1 and 2: Patients who started on placebo continued on placebo after re-randomization

Serious adverse events	Core: FTY720 1.25 mg	Core: FTY720 0.5 mg	Core: Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	38 / 147 (25.85%)	84 / 336 (25.00%)	117 / 487 (24.02%)
number of deaths (all causes)	2	1	2
number of deaths resulting from adverse events	1	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			

subjects affected / exposed	1 / 147 (0.68%)	11 / 336 (3.27%)	9 / 487 (1.85%)
occurrences causally related to treatment / all	1 / 1	12 / 14	6 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
subjects affected / exposed	2 / 147 (1.36%)	1 / 336 (0.30%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysplastic naevus			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fibrous histiocytoma			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 147 (0.68%)	0 / 336 (0.00%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive lobular breast carcinoma			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Lymphocytic leukaemia			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma			

subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma in situ			
subjects affected / exposed	1 / 147 (0.68%)	0 / 336 (0.00%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Medullary thyroid cancer			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melanocytic naevus			
subjects affected / exposed	1 / 147 (0.68%)	0 / 336 (0.00%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to bone			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Metastases to central nervous system			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Metastases to kidney			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Metastases to liver			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Non-Hodgkin's lymphoma			

subjects affected / exposed	1 / 147 (0.68%)	1 / 336 (0.30%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoma			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cancer metastatic			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (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
Prostate cancer			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small cell lung cancer metastatic			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 147 (0.00%)	6 / 336 (1.79%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	8 / 9	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (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
Vascular disorders			
Aneurysm			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arterial spasm			

subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	1 / 147 (0.68%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral artery occlusion			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	1 / 147 (0.68%)	0 / 336 (0.00%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
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 / 147 (0.00%)	4 / 336 (1.19%)	2 / 487 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Raynaud's phenomenon			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Venous thrombosis			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			

subjects affected / exposed	1 / 147 (0.68%)	1 / 336 (0.30%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest discomfort			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device dislocation			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (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
Device occlusion			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (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
Drug ineffective			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gait disturbance			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	1 / 147 (0.68%)	0 / 336 (0.00%)	0 / 487 (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
Non-cardiac chest pain			

subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (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 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Social circumstances			
Activities of daily living impaired			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Poor personal hygiene			
subjects affected / exposed	1 / 147 (0.68%)	0 / 336 (0.00%)	0 / 487 (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
Reproductive system and breast disorders			
Adenomyosis			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adnexal torsion			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
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 / 147 (0.00%)	1 / 336 (0.30%)	2 / 487 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast mass			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Endometriosis			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (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
Prostatitis			
subjects affected / exposed	1 / 147 (0.68%)	0 / 336 (0.00%)	0 / 487 (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
Prostatomegaly			
subjects affected / exposed	1 / 147 (0.68%)	0 / 336 (0.00%)	0 / 487 (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
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopneumopathy			
subjects affected / exposed	1 / 147 (0.68%)	0 / 336 (0.00%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 147 (0.00%)	2 / 336 (0.60%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemothorax			
subjects affected / exposed	1 / 147 (0.68%)	0 / 336 (0.00%)	0 / 487 (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
Nasal obstruction			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pneumonia aspiration			
subjects affected / exposed	1 / 147 (0.68%)	0 / 336 (0.00%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	1 / 147 (0.68%)	0 / 336 (0.00%)	0 / 487 (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 / 147 (0.68%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Respiratory arrest			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sleep apnoea syndrome			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Adjustment disorder			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aggression			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	2 / 487 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depressive symptom			

subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (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
Mania			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mood swings			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Panic attack			
subjects affected / exposed	1 / 147 (0.68%)	0 / 336 (0.00%)	0 / 487 (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
Psychotic disorder			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	2 / 487 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	2 / 487 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood pressure increased			

subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foetal heart rate abnormal			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (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
International normalised ratio decreased			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphocyte count decreased			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Troponin increased			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (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
Weight decreased			
subjects affected / exposed	1 / 147 (0.68%)	0 / 336 (0.00%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alcohol poisoning			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle fracture			

subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clavicle fracture			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Concussion			
subjects affected / exposed	1 / 147 (0.68%)	1 / 336 (0.30%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial bones fracture			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	3 / 147 (2.04%)	1 / 336 (0.30%)	3 / 487 (0.62%)
occurrences causally related to treatment / all	0 / 4	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	1 / 147 (0.68%)	1 / 336 (0.30%)	3 / 487 (0.62%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fibula fracture			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot fracture			

subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (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
Fracture displacement			
subjects affected / exposed	1 / 147 (0.68%)	0 / 336 (0.00%)	0 / 487 (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
Hand fracture			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (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
Hip fracture			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	1 / 147 (0.68%)	0 / 336 (0.00%)	2 / 487 (0.41%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint dislocation			
subjects affected / exposed	1 / 147 (0.68%)	0 / 336 (0.00%)	2 / 487 (0.41%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laceration			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (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
Limb traumatic amputation			

subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
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 vertebral fracture			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
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 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax traumatic			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural complication			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haematoma			
subjects affected / exposed	1 / 147 (0.68%)	0 / 336 (0.00%)	0 / 487 (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
Post procedural haemorrhage			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (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
Radius fracture			

subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (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
Rib fracture			
subjects affected / exposed	1 / 147 (0.68%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skull fracture			
subjects affected / exposed	1 / 147 (0.68%)	0 / 336 (0.00%)	0 / 487 (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
Subdural haematoma			
subjects affected / exposed	1 / 147 (0.68%)	0 / 336 (0.00%)	0 / 487 (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
Thermal burn			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
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 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (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
Traumatic renal injury			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
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 limb fracture			

subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound			
subjects affected / exposed	1 / 147 (0.68%)	0 / 336 (0.00%)	0 / 487 (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
Wound dehiscence			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist fracture			
subjects affected / exposed	1 / 147 (0.68%)	0 / 336 (0.00%)	0 / 487 (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
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (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
Atrial fibrillation			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (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
Atrioventricular block			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			

subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block first degree			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block second degree			
subjects affected / exposed	1 / 147 (0.68%)	1 / 336 (0.30%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	2 / 147 (1.36%)	2 / 336 (0.60%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	2 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	1 / 147 (0.68%)	0 / 336 (0.00%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (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
Pericarditis			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus bradycardia			

subjects affected / exposed	1 / 147 (0.68%)	0 / 336 (0.00%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia paroxysmal			
subjects affected / exposed	1 / 147 (0.68%)	0 / 336 (0.00%)	0 / 487 (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
Nervous system disorders			
Aphasia			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (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
Arachnoiditis			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain oedema			
subjects affected / exposed	1 / 147 (0.68%)	0 / 336 (0.00%)	0 / 487 (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
Central nervous system lesion			
subjects affected / exposed	1 / 147 (0.68%)	0 / 336 (0.00%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	2 / 487 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular disorder			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Convulsion			

subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (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
Monoparesis			
subjects affected / exposed	1 / 147 (0.68%)	0 / 336 (0.00%)	0 / 487 (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 sclerosis			
subjects affected / exposed	2 / 147 (1.36%)	3 / 336 (0.89%)	5 / 487 (1.03%)
occurrences causally related to treatment / all	1 / 2	1 / 3	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple sclerosis relapse			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	5 / 487 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle spasticity			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myelitis transverse			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuralgia			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nystagmus			

subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
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 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraparesis			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (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
Peroneal nerve palsy			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	1 / 147 (0.68%)	0 / 336 (0.00%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Primary progressive multiple sclerosis			
subjects affected / exposed	1 / 147 (0.68%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Progressive multiple sclerosis			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Quadriparesis			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			

subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (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
Seizure			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Status epilepticus			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	2 / 487 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Trigeminal neuralgia			
subjects affected / exposed	1 / 147 (0.68%)	0 / 336 (0.00%)	0 / 487 (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
Uhthoff's phenomenon			
subjects affected / exposed	2 / 147 (1.36%)	0 / 336 (0.00%)	0 / 487 (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
VIIth nerve paralysis			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
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 and lymphatic system disorders			
Anaemia macrocytic			

subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphadenopathy			
subjects affected / exposed	1 / 147 (0.68%)	1 / 336 (0.30%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Amblyopia strabismic			
subjects affected / exposed	1 / 147 (0.68%)	0 / 336 (0.00%)	0 / 487 (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
Angle closure glaucoma			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract cortical			
subjects affected / exposed	1 / 147 (0.68%)	0 / 336 (0.00%)	0 / 487 (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
Chorioretinopathy			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystoid macular oedema			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diplopia			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intraocular haematoma			

subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
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	1 / 147 (0.68%)	4 / 336 (1.19%)	4 / 487 (0.82%)
occurrences causally related to treatment / all	2 / 2	4 / 4	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myopia			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (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
Optic atrophy			
subjects affected / exposed	1 / 147 (0.68%)	0 / 336 (0.00%)	0 / 487 (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
Retinal detachment			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal tear			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (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
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
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 lower			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (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
Anal polyp			

subjects affected / exposed	1 / 147 (0.68%)	0 / 336 (0.00%)	0 / 487 (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
Colitis ulcerative			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 147 (0.00%)	2 / 336 (0.60%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Faecaloma			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	1 / 487 (0.21%)
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			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (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
Inguinal hernia			
subjects affected / exposed	1 / 147 (0.68%)	0 / 336 (0.00%)	2 / 487 (0.41%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
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 / 147 (0.00%)	0 / 336 (0.00%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstruction gastric			

subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (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
Pancreatitis			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (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
Pancreatitis acute			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (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
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 147 (0.68%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	3 / 487 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis obstructive			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			

Actinic keratosis			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alopecia			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decubitus ulcer			
subjects affected / exposed	1 / 147 (0.68%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jessner's lymphocytic infiltration			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lentigo			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Bladder neck sclerosis			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (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
Nephrogenic diabetes insipidus			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			

subjects affected / exposed	1 / 147 (0.68%)	2 / 336 (0.60%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neurogenic bladder			
subjects affected / exposed	1 / 147 (0.68%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polyuria			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
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 failure			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure acute			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	2 / 487 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urethral obstruction			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary incontinence			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (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
Urinary retention			
subjects affected / exposed	0 / 147 (0.00%)	2 / 336 (0.60%)	0 / 487 (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
Endocrine disorders			
Hypothyroidism			

subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	2 / 487 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (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
Bone swelling			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bursitis			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc disorder			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (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
Joint swelling			
subjects affected / exposed	1 / 147 (0.68%)	0 / 336 (0.00%)	0 / 487 (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
Mobility decreased			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	2 / 487 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			

subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	2 / 487 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteopenia			
subjects affected / exposed	1 / 147 (0.68%)	0 / 336 (0.00%)	0 / 487 (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
Pain in extremity			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhabdomyolysis			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	2 / 487 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sjogren's syndrome			
subjects affected / exposed	1 / 147 (0.68%)	0 / 336 (0.00%)	0 / 487 (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
Spinal column stenosis			
subjects affected / exposed	1 / 147 (0.68%)	0 / 336 (0.00%)	0 / 487 (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
Tendon disorder			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (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			
Appendicitis			

subjects affected / exposed	1 / 147 (0.68%)	0 / 336 (0.00%)	2 / 487 (0.41%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial infection			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blister infected			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis viral			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopneumonia			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bursitis infective			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	1 / 147 (0.68%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dengue fever			

subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
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 / 147 (0.00%)	0 / 336 (0.00%)	2 / 487 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis bacterial			
subjects affected / exposed	1 / 147 (0.68%)	0 / 336 (0.00%)	0 / 487 (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
Epididymitis			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (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
Gastroenteritis			
subjects affected / exposed	0 / 147 (0.00%)	2 / 336 (0.60%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
H1N1 influenza			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	2 / 487 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	1 / 147 (0.68%)	2 / 336 (0.60%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	1 / 1	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster infection neurological			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster meningomyelitis			

subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incision site infection			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (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
Infection			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious pleural effusion			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 147 (0.00%)	3 / 336 (0.89%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myelitis			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (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
Ophthalmic herpes simplex			
subjects affected / exposed	1 / 147 (0.68%)	0 / 336 (0.00%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			

subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	2 / 147 (1.36%)	4 / 336 (1.19%)	2 / 487 (0.41%)
occurrences causally related to treatment / all	0 / 3	3 / 4	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary sepsis			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	3 / 487 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (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 tract infection			
subjects affected / exposed	1 / 147 (0.68%)	0 / 336 (0.00%)	0 / 487 (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
Septic shock			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Serratia sepsis			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous abscess			

subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic mycosis			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheobronchitis			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	2 / 147 (1.36%)	8 / 336 (2.38%)	12 / 487 (2.46%)
occurrences causally related to treatment / all	0 / 4	3 / 9	3 / 18
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection bacterial			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	1 / 147 (0.68%)	0 / 336 (0.00%)	2 / 487 (0.41%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			

subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	2 / 487 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 147 (0.00%)	1 / 336 (0.30%)	0 / 487 (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
Polydipsia			
subjects affected / exposed	0 / 147 (0.00%)	0 / 336 (0.00%)	1 / 487 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Extension: FTY1.25-0.5	Extension: FTY0.5-0.5	Extension: Placebo-FTY0.5
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 74 (9.46%)	10 / 196 (5.10%)	37 / 301 (12.29%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 74 (1.35%)	2 / 196 (1.02%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	2 / 2	0 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			

subjects affected / exposed	1 / 74 (1.35%)	0 / 196 (0.00%)	0 / 301 (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
Dysplastic naevus			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fibrous histiocytoma			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive lobular breast carcinoma			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphocytic leukaemia			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma in situ			

subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Medullary thyroid cancer			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melanocytic naevus			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to bone			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to central nervous system			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to kidney			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to liver			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-Hodgkin's lymphoma			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoma			

subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cancer metastatic			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small cell lung cancer metastatic			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aneurysm			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arterial spasm			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			

subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral artery occlusion			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral venous disease			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Raynaud's phenomenon			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Venous thrombosis			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest discomfort			

subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device dislocation			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device occlusion			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug ineffective			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gait disturbance			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			

subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Social circumstances			
Activities of daily living impaired			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Poor personal hygiene			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Adenomyosis			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adnexal torsion			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast mass			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometriosis			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Prostatitis			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostatomegaly			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopneumopathy			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemothorax			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal obstruction			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pneumothorax			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	1 / 301 (0.33%)
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	0 / 74 (0.00%)	0 / 196 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sleep apnoea syndrome			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Adjustment disorder			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aggression			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 74 (0.00%)	1 / 196 (0.51%)	0 / 301 (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
Depressive symptom			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mania			

subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mood swings			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Panic attack			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic disorder			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood pressure increased			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foetal heart rate abnormal			

subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
International normalised ratio decreased			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphocyte count decreased			
subjects affected / exposed	1 / 74 (1.35%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Troponin increased			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alcohol poisoning			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle fracture			
subjects affected / exposed	0 / 74 (0.00%)	1 / 196 (0.51%)	0 / 301 (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
Clavicle fracture			

subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Concussion			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial bones fracture			
subjects affected / exposed	0 / 74 (0.00%)	1 / 196 (0.51%)	0 / 301 (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 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fibula fracture			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	1 / 301 (0.33%)
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 fracture			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture displacement			

subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hand fracture			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint dislocation			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laceration			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Limb traumatic amputation			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar vertebral fracture			

subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscus injury			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax traumatic			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural complication			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haematoma			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			

subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skull fracture			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thermal burn			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic renal injury			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound			

subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound dehiscence			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist fracture			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block first degree			

subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block second degree			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus bradycardia			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia paroxysmal			

subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Aphasia			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arachnoiditis			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain oedema			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Central nervous system lesion			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular disorder			
subjects affected / exposed	1 / 74 (1.35%)	0 / 196 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Convulsion			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised tonic-clonic seizure			

subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Monoparesis			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple sclerosis			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	2 / 301 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple sclerosis relapse			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	2 / 301 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle spasticity			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myelitis transverse			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuralgia			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nystagmus			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Optic neuritis			

subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraparesis			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peroneal nerve palsy			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Primary progressive multiple sclerosis			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Progressive multiple sclerosis			
subjects affected / exposed	0 / 74 (0.00%)	1 / 196 (0.51%)	0 / 301 (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
Quadriparesis			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			

subjects affected / exposed	0 / 74 (0.00%)	1 / 196 (0.51%)	0 / 301 (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
Status epilepticus			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Trigeminal neuralgia			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uhthoff's phenomenon			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VIIth nerve paralysis			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia macrocytic			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphadenopathy			

subjects affected / exposed	0 / 74 (0.00%)	1 / 196 (0.51%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Amblyopia strabismic			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angle closure glaucoma			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract cortical			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chorioretinopathy			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystoid macular oedema			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diplopia			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intraocular haematoma			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Macular oedema			

subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myopia			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Optic atrophy			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal detachment			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal tear			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain lower			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal polyp			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ulcerative			

subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Faecaloma			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstruction gastric			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			

subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis obstructive			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alopecia			

subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decubitus ulcer			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jessner's lymphocytic infiltration			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lentigo			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Bladder neck sclerosis			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrogenic diabetes insipidus			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 74 (0.00%)	1 / 196 (0.51%)	0 / 301 (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
Neurogenic bladder			

subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polyuria			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure acute			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urethral obstruction			
subjects affected / exposed	0 / 74 (0.00%)	1 / 196 (0.51%)	0 / 301 (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
Urinary incontinence			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	2 / 301 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone swelling			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bursitis			
subjects affected / exposed	1 / 74 (1.35%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc disorder			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint swelling			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mobility decreased			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	1 / 74 (1.35%)	0 / 196 (0.00%)	2 / 301 (0.66%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			

subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteopenia			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhabdomyolysis			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sjogren's syndrome			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal column stenosis			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon disorder			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial infection			

subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blister infected			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis viral			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopneumonia			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bursitis infective			
subjects affected / exposed	1 / 74 (1.35%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 74 (1.35%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	0 / 74 (0.00%)	1 / 196 (0.51%)	0 / 301 (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
Dengue fever			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			

subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis bacterial			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epididymitis			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	1 / 301 (0.33%)
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			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
H1N1 influenza			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster infection neurological			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster meningomyelitis			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incision site infection			

subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious pleural effusion			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myelitis			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ophthalmic herpes simplex			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			

subjects affected / exposed	1 / 74 (1.35%)	0 / 196 (0.00%)	1 / 301 (0.33%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary sepsis			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Serratia sepsis			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous abscess			
subjects affected / exposed	1 / 74 (1.35%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic mycosis			

subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheobronchitis			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 74 (1.35%)	0 / 196 (0.00%)	4 / 301 (1.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection bacterial			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 74 (0.00%)	1 / 196 (0.51%)	0 / 301 (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
Viral infection			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral upper respiratory tract infection			

subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polydipsia			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	0 / 301 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
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	Core: FTY720 1.25 mg	Core: FTY720 0.5 mg	Core: Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	132 / 147 (89.80%)	278 / 336 (82.74%)	406 / 487 (83.37%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Seborrhoeic keratosis			
subjects affected / exposed	10 / 147 (6.80%)	12 / 336 (3.57%)	14 / 487 (2.87%)
occurrences (all)	10	14	17
Melanocytic naevus			
subjects affected / exposed	21 / 147 (14.29%)	16 / 336 (4.76%)	31 / 487 (6.37%)
occurrences (all)	28	19	34
Vascular disorders			
Hypertension			
subjects affected / exposed	23 / 147 (15.65%)	43 / 336 (12.80%)	28 / 487 (5.75%)
occurrences (all)	24	46	29
General disorders and administration site conditions			

Gait disturbance			
subjects affected / exposed	10 / 147 (6.80%)	15 / 336 (4.46%)	24 / 487 (4.93%)
occurrences (all)	12	16	31
Fatigue			
subjects affected / exposed	16 / 147 (10.88%)	24 / 336 (7.14%)	43 / 487 (8.83%)
occurrences (all)	19	26	44
Pyrexia			
subjects affected / exposed	8 / 147 (5.44%)	18 / 336 (5.36%)	20 / 487 (4.11%)
occurrences (all)	10	22	22
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	8 / 147 (5.44%)	28 / 336 (8.33%)	34 / 487 (6.98%)
occurrences (all)	9	31	38
Dyspnoea			
subjects affected / exposed	8 / 147 (5.44%)	14 / 336 (4.17%)	16 / 487 (3.29%)
occurrences (all)	9	18	16
Psychiatric disorders			
Depression			
subjects affected / exposed	11 / 147 (7.48%)	15 / 336 (4.46%)	37 / 487 (7.60%)
occurrences (all)	11	16	38
Insomnia			
subjects affected / exposed	8 / 147 (5.44%)	12 / 336 (3.57%)	29 / 487 (5.95%)
occurrences (all)	8	14	32
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	17 / 147 (11.56%)	39 / 336 (11.61%)	7 / 487 (1.44%)
occurrences (all)	18	54	9
Blood cholesterol increased			
subjects affected / exposed	8 / 147 (5.44%)	15 / 336 (4.46%)	16 / 487 (3.29%)
occurrences (all)	8	18	17
Gamma-glutamyltransferase increased			
subjects affected / exposed	19 / 147 (12.93%)	31 / 336 (9.23%)	3 / 487 (0.62%)
occurrences (all)	24	44	4
Injury, poisoning and procedural complications			

Fall			
subjects affected / exposed	31 / 147 (21.09%)	47 / 336 (13.99%)	91 / 487 (18.69%)
occurrences (all)	43	85	159
Nervous system disorders			
Dizziness			
subjects affected / exposed	10 / 147 (6.80%)	19 / 336 (5.65%)	29 / 487 (5.95%)
occurrences (all)	12	21	34
Headache			
subjects affected / exposed	28 / 147 (19.05%)	56 / 336 (16.67%)	77 / 487 (15.81%)
occurrences (all)	35	86	105
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	13 / 147 (8.84%)	19 / 336 (5.65%)	0 / 487 (0.00%)
occurrences (all)	28	31	0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	3 / 147 (2.04%)	17 / 336 (5.06%)	12 / 487 (2.46%)
occurrences (all)	3	18	13
Constipation			
subjects affected / exposed	10 / 147 (6.80%)	27 / 336 (8.04%)	35 / 487 (7.19%)
occurrences (all)	11	28	38
Diarrhoea			
subjects affected / exposed	13 / 147 (8.84%)	15 / 336 (4.46%)	18 / 487 (3.70%)
occurrences (all)	14	16	22
Nausea			
subjects affected / exposed	14 / 147 (9.52%)	21 / 336 (6.25%)	19 / 487 (3.90%)
occurrences (all)	16	26	22
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	8 / 147 (5.44%)	15 / 336 (4.46%)	19 / 487 (3.90%)
occurrences (all)	9	16	20
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	13 / 147 (8.84%)	30 / 336 (8.93%)	48 / 487 (9.86%)
occurrences (all)	16	38	54
Back pain			

subjects affected / exposed	16 / 147 (10.88%)	36 / 336 (10.71%)	75 / 487 (15.40%)
occurrences (all)	19	43	88
Pain in extremity			
subjects affected / exposed	9 / 147 (6.12%)	21 / 336 (6.25%)	35 / 487 (7.19%)
occurrences (all)	10	26	40
Infections and infestations			
Bronchitis			
subjects affected / exposed	10 / 147 (6.80%)	16 / 336 (4.76%)	21 / 487 (4.31%)
occurrences (all)	16	19	25
Cystitis			
subjects affected / exposed	10 / 147 (6.80%)	9 / 336 (2.68%)	17 / 487 (3.49%)
occurrences (all)	13	10	27
Gastroenteritis			
subjects affected / exposed	10 / 147 (6.80%)	12 / 336 (3.57%)	22 / 487 (4.52%)
occurrences (all)	12	12	23
Influenza			
subjects affected / exposed	14 / 147 (9.52%)	26 / 336 (7.74%)	43 / 487 (8.83%)
occurrences (all)	17	33	67
Nasopharyngitis			
subjects affected / exposed	40 / 147 (27.21%)	78 / 336 (23.21%)	135 / 487 (27.72%)
occurrences (all)	61	132	216
Upper respiratory tract infection			
subjects affected / exposed	21 / 147 (14.29%)	37 / 336 (11.01%)	57 / 487 (11.70%)
occurrences (all)	42	57	91
Urinary tract infection			
subjects affected / exposed	21 / 147 (14.29%)	47 / 336 (13.99%)	75 / 487 (15.40%)
occurrences (all)	48	112	139
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	10 / 147 (6.80%)	13 / 336 (3.87%)	19 / 487 (3.90%)
occurrences (all)	11	18	20

Non-serious adverse events	Extension: FTY1.25-0.5	Extension: FTY0.5-0.5	Extension: Placebo-FTY0.5
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 74 (58.11%)	70 / 196 (35.71%)	138 / 301 (45.85%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Seborrhoeic keratosis			
subjects affected / exposed	1 / 74 (1.35%)	3 / 196 (1.53%)	4 / 301 (1.33%)
occurrences (all)	1	3	4
Melanocytic naevus			
subjects affected / exposed	4 / 74 (5.41%)	3 / 196 (1.53%)	9 / 301 (2.99%)
occurrences (all)	5	3	10
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 74 (2.70%)	5 / 196 (2.55%)	18 / 301 (5.98%)
occurrences (all)	3	5	18
General disorders and administration site conditions			
Gait disturbance			
subjects affected / exposed	0 / 74 (0.00%)	1 / 196 (0.51%)	0 / 301 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	0 / 74 (0.00%)	1 / 196 (0.51%)	9 / 301 (2.99%)
occurrences (all)	0	1	9
Pyrexia			
subjects affected / exposed	3 / 74 (4.05%)	0 / 196 (0.00%)	4 / 301 (1.33%)
occurrences (all)	3	0	5
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 74 (2.70%)	1 / 196 (0.51%)	4 / 301 (1.33%)
occurrences (all)	2	1	4
Dyspnoea			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	1 / 301 (0.33%)
occurrences (all)	0	0	1
Psychiatric disorders			
Depression			
subjects affected / exposed	2 / 74 (2.70%)	2 / 196 (1.02%)	4 / 301 (1.33%)
occurrences (all)	2	3	4
Insomnia			
subjects affected / exposed	1 / 74 (1.35%)	4 / 196 (2.04%)	7 / 301 (2.33%)
occurrences (all)	1	4	7
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	0 / 74 (0.00%)	1 / 196 (0.51%)	6 / 301 (1.99%)
occurrences (all)	0	1	6
Blood cholesterol increased			
subjects affected / exposed	0 / 74 (0.00%)	1 / 196 (0.51%)	3 / 301 (1.00%)
occurrences (all)	0	1	3
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 74 (0.00%)	3 / 196 (1.53%)	5 / 301 (1.66%)
occurrences (all)	0	3	5
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	6 / 74 (8.11%)	5 / 196 (2.55%)	13 / 301 (4.32%)
occurrences (all)	9	8	15
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 74 (2.70%)	0 / 196 (0.00%)	2 / 301 (0.66%)
occurrences (all)	2	0	2
Headache			
subjects affected / exposed	3 / 74 (4.05%)	3 / 196 (1.53%)	13 / 301 (4.32%)
occurrences (all)	3	4	13
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	4 / 74 (5.41%)	7 / 196 (3.57%)	11 / 301 (3.65%)
occurrences (all)	4	7	11
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 74 (0.00%)	1 / 196 (0.51%)	2 / 301 (0.66%)
occurrences (all)	0	1	2
Constipation			
subjects affected / exposed	0 / 74 (0.00%)	2 / 196 (1.02%)	6 / 301 (1.99%)
occurrences (all)	0	2	6
Diarrhoea			
subjects affected / exposed	1 / 74 (1.35%)	3 / 196 (1.53%)	1 / 301 (0.33%)
occurrences (all)	1	3	1
Nausea			

subjects affected / exposed	2 / 74 (2.70%)	1 / 196 (0.51%)	4 / 301 (1.33%)
occurrences (all)	3	1	4
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	2 / 74 (2.70%)	1 / 196 (0.51%)	6 / 301 (1.99%)
occurrences (all)	2	1	6
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 74 (4.05%)	3 / 196 (1.53%)	8 / 301 (2.66%)
occurrences (all)	3	3	8
Back pain			
subjects affected / exposed	5 / 74 (6.76%)	5 / 196 (2.55%)	10 / 301 (3.32%)
occurrences (all)	5	5	12
Pain in extremity			
subjects affected / exposed	3 / 74 (4.05%)	3 / 196 (1.53%)	3 / 301 (1.00%)
occurrences (all)	3	3	3
Infections and infestations			
Bronchitis			
subjects affected / exposed	3 / 74 (4.05%)	2 / 196 (1.02%)	1 / 301 (0.33%)
occurrences (all)	3	2	2
Cystitis			
subjects affected / exposed	0 / 74 (0.00%)	0 / 196 (0.00%)	2 / 301 (0.66%)
occurrences (all)	0	0	2
Gastroenteritis			
subjects affected / exposed	0 / 74 (0.00%)	3 / 196 (1.53%)	3 / 301 (1.00%)
occurrences (all)	0	3	3
Influenza			
subjects affected / exposed	3 / 74 (4.05%)	4 / 196 (2.04%)	9 / 301 (2.99%)
occurrences (all)	3	4	9
Nasopharyngitis			
subjects affected / exposed	9 / 74 (12.16%)	10 / 196 (5.10%)	23 / 301 (7.64%)
occurrences (all)	14	11	27
Upper respiratory tract infection			
subjects affected / exposed	6 / 74 (8.11%)	6 / 196 (3.06%)	14 / 301 (4.65%)
occurrences (all)	6	6	14
Urinary tract infection			

subjects affected / exposed occurrences (all)	4 / 74 (5.41%) 6	11 / 196 (5.61%) 15	25 / 301 (8.31%) 40
Metabolism and nutrition disorders Hypercholesterolaemia subjects affected / exposed occurrences (all)	4 / 74 (5.41%) 4	4 / 196 (2.04%) 4	5 / 301 (1.66%) 5

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 June 2008	Amendment was issued to implement safety-related guidance to reinforce theNecessity for vigilance with infections, to implement guidance aimed at reducing the risk of serious infection, and to provide more specific guidance regarding the monitoring and follow-up of patients diagnosed with macular edema.
01 August 2008	Amendment was issued to implement additional safety measures following input from regulatory authorities and infectious disease experts
01 March 2009	Amendment was created to reflect procedural changes in the central review of the diagnostic criteria for PPMS for all patients prior to randomization. In addition, additional laboratory parameters were added including: blood urea nitrogen (BUN) and serum electrolytes including sodium, potassium, chloride, calcium, magnesium and phosphate.
03 August 2009	Amendment was issued to reflect the addition of echocardiograms to the protocol safety assessments at selected sites to evaluate potential long-term exposure effects on the cardiovascular system following treatment with fingolimod. The informed consent for patients was revised to include collection of new echocardiography data.
02 November 2009	Amendment was issued to reflect the decision made by Novartis, following the DSMB recommendation, to discontinue the fingolimod 1.25 mg treatment arm from all studies in the fingolimod MS clinical development program. The decision resulted in a switch for previously enrolled patients receiving fingolimod 1.25 mg/day to fingolimod 0.5 mg/day. In addition, this amendment:Corrected electrolyte notable values for potassium, BUN and magnesium, Added further guidance for central testing of safety monitoring for low lymphocytes.
01 September 2010	Amendment was issued to introduce an optional MRI sub-study to the D2306 protocol. Due to delayed implementation, the number of patients available to participate in the sub-study was too small to provide meaningful data and was subsequently removed in Amendment 8. The cut off values for central foveal thickness by OCT leading to fluorescein angiography in the ophthalmic monitoring guideline was also updated to accommodate the current normal ranges in new generation OCT machines
01 February 2012	Amendment was issued to outline additional requirements during the first dose observation period. A pre-dose ECG was added to help detect potential risk factors, in particular atrio-ventricular (AV) conduction and rhythm disorders. The 6-hour ECG was added to detect otherwise asymptomatic electrocardiographic events (specifically conduction delays) prior to discharging the patient from the clinic. Continued observation beyond 6 hours was required for patients who, at the end of the first-dose observation period, had a heart rate < 45 bpm, or new-onset second-degree or higher
01 June 2012	Amendment introduced an open-label, single-arm, long-term extension to Study D2306, updated revised safety monitoring, and removed the MRI sub-study introduced in Amendment 6. This amendment implemented the transition of patients in Cohort 1 to the extension study once it was initiated at their respective sites. Cohort 2 patients were eligible to enroll in the extension study when the last patient enrolled in the study had completed 36 months of treatment or the patient had reached the maximum treatment duration of 5 years.

02 February 2014	Amendment was issued to address comments from FDA regarding the methodology for the statistical analysis of the primary and secondary efficacy endpoints. The following changes were made: the primary analysis of the primary endpoint was updated from the WLW method to the Cox proportional hazards model, the time to 3-month sustained disability progression based on the time taken to complete the 25'TWT or 9-HPT were removed as key secondary endpoints, and the percent change from Baseline in brain volume was added as a key secondary endpoint.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.nov for complete trial results.

Notes: