Clinical trial results:
A multicenter, randomized, double-blind, parallel-group, placebo-controlled variable treatment duration study evaluating the efficacy and safety of Siponimod (BAF312) in patients with secondary progressive multiple sclerosis followed by extended treatment with open-label BAF312

Summary

EudraCT number	2012-003056-36
Trial protocol	HU IE DE CZ SK NL ES GB AT SE PT IT LV GR LT EE BE PL BG FR
Global end of trial date	31 March 2023
Results information	
Result version number	v1
This version publication date	12 April 2024
First version publication date	12 April 2024

Trial information

Trial identification	
Sponsor protocol code	CBAF312A2304
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01665144
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	Novartis campus, Basel, Switzerland, CH-4056
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, novartis.email@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	31 March 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 March 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to demonstrate the efficacy of BAF312 relative to placebo in delaying the time to 3-month confirmed disability progression in patients with secondary progressive multiple sclerosis (SPMS) as measured by Expanded Disability Status Scale (EDSS) in the Core Part of the study.

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	20 December 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	10 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 30
Country: Number of subjects enrolled	Australia: 36
Country: Number of subjects enrolled	Austria: 59
Country: Number of subjects enrolled	Belgium: 34
Country: Number of subjects enrolled	Bulgaria: 30
Country: Number of subjects enrolled	Canada: 47
Country: Number of subjects enrolled	China: 22
Country: Number of subjects enrolled	Czechia: 35
Country: Number of subjects enrolled	Estonia: 16
Country: Number of subjects enrolled	France: 85
Country: Number of subjects enrolled	Germany: 257
Country: Number of subjects enrolled	Greece: 14
Country: Number of subjects enrolled	Hungary: 60
Country: Number of subjects enrolled	Ireland: 11
Country: Number of subjects enrolled	Israel: 16
Country: Number of subjects enrolled	Italy: 89
Country: Number of subjects enrolled	Japan: 23

Country: Number of subjects enrolled	Latvia: 19
Country: Number of subjects enrolled	Lithuania: 25
Country: Number of subjects enrolled	Netherlands: 33
Country: Number of subjects enrolled	Poland: 109
Country: Number of subjects enrolled	Portugal: 33
Country: Number of subjects enrolled	Romania: 22
Country: Number of subjects enrolled	Russian Federation: 95
Country: Number of subjects enrolled	Slovakia: 25
Country: Number of subjects enrolled	Spain: 106
Country: Number of subjects enrolled	Sweden: 24
Country: Number of subjects enrolled	Switzerland: 31
Country: Number of subjects enrolled	Türkiye: 33
Country: Number of subjects enrolled	United Kingdom: 78
Country: Number of subjects enrolled	United States: 154
Worldwide total number of subjects	1651
EEA total number of subjects	1086

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)	1651
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in 294 investigative sites in 31 countries.

Pre-assignment

Screening details:

The Screening Epoch included a Screening Phase (Day -45 to Day -8) and a Baseline Phase (Day -7 to Day 1 before the first study drug administration). During the Core Part, eligible patients were randomized in a 2:1 ratio to siponimod (BAF312) or placebo. Patients who were eligible to enter the Extension Part received open label siponimod.

Period 1

Period 1 title	Core Part
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	Siponimod (BAF312)

Arm description:

Participants started on Day 1 and were uptitrated from 0.25 mg to 2 mg of BAF312 orally over a period of 6 days. After Day 7, participants continued on 2 mg BAF312 daily for a variable duration.

Arm type	Experimental
Investigational medicinal product name	Siponimod
Investigational medicinal product code	BAF312
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Following randomization in the Core Part (CP), patients underwent 6-day titration to the target maintenance dose of blinded study drug (2 mg siponimod). Patients with lymphocyte counts (at 2 consecutive visits) of <0.2 x10^9/L were to reduce the dose to 1 mg/day in a blinded fashion. Siponimod was administered orally once daily as film-coated tablets.

Arm title	Placebo

Arm description:

Matching placebo to BAF312 was administered orally during the Core Part of the trial.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Following randomization in the Core Part (CP), patients underwent 6-day titration to the target maintenance dose of blinded study drug (placebo).
Placebo was administered orally once daily as film-coated tablets.

Number of subjects in period 1	Siponimod (BAF312)	Placebo
Started	1105	546
Safety set	1099	546
Full analysis set	1099	546
Completed	903	424
Not completed	202	122
Physician decision	13	1
Adverse Event	45	18
Technical problems	2	-
Death	3	1
Non-compliance with study treatment	5	-
Protocol deviation	3	1
Lost to follow-up	9	8
Progressive disease	8	4
New therapy for study indication	2	1
Withdrawal by subject	96	77
Lack of efficacy	16	11

Period 2

Period 2 title	Extension Part
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Siponimod (BAF312)

Arm description:

Participants started on Day 1 and were uptitrated from 0.25 mg to 2 mg of BAF312 orally over a period of 6 days. After Day 7, participants continued on 2 mg BAF312 daily for a variable duration.

Arm type	Experimental
Investigational medicinal product name	Siponimod
Investigational medicinal product code	BAF312
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Eligible patients who entered the Extension Part (EP) received open label siponimod. For the EP, treatment for patients who had completed the CP on either double-blind treatment or on the abbreviated schedule, initiated with the 6-day dose titration pack. Patients who had been on 2 mg with double-blind treatment were titrated to the 2 mg dose while patients who were taking 1 mg were titrated to the 1 mg dose. Patients who had been on open-label siponimod in the CP initiated treatment on their current dose of siponimod.

Arm title	Placebo-BAF312

Arm description:

Participants who received placebo in the Core Part and switched to siponimod in the Extension Part.

Arm type	Experimental
Investigational medicinal product name	Siponimod
Investigational medicinal product code	BAF312
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Eligible patients who entered the Extension Part (EP) received open label siponimod. For the EP, treatment for patients who had completed the CP on either double-blind treatment or on the abbreviated schedule, initiated with the 6-day dose titration pack. Patients who had been on 2 mg with double-blind treatment were titrated to the 2 mg dose while patients who were taking 1 mg were titrated to the 1 mg dose. Patients who had been on open-label siponimod in the CP initiated treatment on their current dose of siponimod.

Number of subjects in period 2[1]	Siponimod (BAF312)	Placebo-BAF312
Started	821	399
Completed	326	159
Not completed	495	240
Physician decision	29	13
Adverse Event	104	59
Technical problems	20	8
Death	20	4
Protocol deviation	3	-
Study terminated by sponsor	42	19
Patient/guardian decision	180	98
Progressive disease	36	14
Lost to follow-up	9	5
Missing	12	6
New therapy for study indication	3	2
Lack of efficacy	37	12

Notes:

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

Justification: Eligible patients started the Extension Part

Baseline characteristics

Reporting groups	
Reporting group title	Siponimod (BAF312)
Reporting group description:	
Participants started on Day 1 and were uptitrated from 0.25 mg to 2 mg of BAF312 orally over a period of 6 days. After Day 7, participants continued on 2 mg BAF312 daily for a variable duration.	
Reporting group title	Placebo
Reporting group description:	
Matching placebo to BAF312 was administered orally during the Core Part of the trial.	

Reporting group values	Siponimod (BAF312)	Placebo	Total
Number of subjects	1105	546	1651
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	1105	546	1651
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous			
Units: Years			
arithmetic mean	48.0	48.1	
standard deviation	± 7.84	± 7.94	-
Sex: Female, Male			
Units: Participants			
Female	669	323	992
Male	436	223	659
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	31	18	49
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	7	3	10
White	1050	513	1563
More than one race	0	0	0
Unknown or Not Reported	17	12	29

End points

End points reporting groups

Reporting group title	Siponimod (BAF312)
Reporting group description:	
Participants started on Day 1 and were uptitrated from 0.25 mg to 2 mg of BAF312 orally over a period of 6 days. After Day 7, participants continued on 2 mg BAF312 daily for a variable duration.	
Reporting group title	Placebo
Reporting group description:	
Matching placebo to BAF312 was administered orally during the Core Part of the trial.	
Reporting group title	Siponimod (BAF312)
Reporting group description:	
Participants started on Day 1 and were uptitrated from 0.25 mg to 2 mg of BAF312 orally over a period of 6 days. After Day 7, participants continued on 2 mg BAF312 daily for a variable duration.	
Reporting group title	Placebo-BAF312
Reporting group description:	
Participants who received placebo in the Core Part and switched to siponimod in the Extension Part.	

Primary: Percentage of participants with 3-month Confirmed Disability Progression (CDP) events as measured by the Expanded Disability Status Scale (EDSS)

End point title	Percentage of participants with 3-month Confirmed Disability Progression (CDP) events as measured by the Expanded Disability Status Scale (EDSS)
End point description:	
The EDSS uses an ordinal scale to assess neurologic impairment in MS based on a neurological examination. Scores in each of 7 functional systems (Visual, Brain Stem, Pyramidal, Cerebellar, Sensory, Bowel & Bladder, and Cerebral) and an ambulation score were combined to determine the EDSS steps, ranging from 0 (normal) to 10 (death due to MS). 3-month confirmed disability progression is defined as an increase of score of 1 point in patients with baseline score of 3.0 to 5.0 and 0.5 point increase with baseline score of 5.5 to 6.5 sustained for at least 3 months.	
End point type	Primary
End point timeframe:	
Baseline, every 3 month up to the maximum of approximately 3 years	

End point values	Siponimod (BAF312)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1096	545		
Units: Percentage of participants				
number (not applicable)	26.3	31.7		

Statistical analyses

Statistical analysis title	3-month confirmed disability progression
Comparison groups	Placebo v Siponimod (BAF312)

Number of subjects included in analysis	1641
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0134
Method	Cox proportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	0.95

Secondary: Percentage of participants with 3-month confirmed worsening in T25W of at least 20% from baseline

End point title	Percentage of participants with 3-month confirmed worsening in T25W of at least 20% from baseline

End point description:

The Timed 25-Foot Walk Test (T25W) measured the time, in seconds, to walk 25 feet (7.62 meters).
A 3-month confirmed worsening of at least 20% from baseline in the T25W was defined as an increase from baseline sustained for at least 3 months.
This outcome measure was analyzed using a Cox proportional hazards model.

End point type	Secondary

End point timeframe:

Baseline, every 3 months up to the maximum of approximately 3 years

End point values	Siponimod (BAF312)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1087	543		
Units: Percentage of participants				
number (not applicable)	39.7	41.4		

Statistical analyses

Statistical analysis title	3-month confirmed worsening T25W
Comparison groups	Siponimod (BAF312) v Placebo
Number of subjects included in analysis	1630
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.4398
Method	Cox proportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.94

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.1

Secondary: Change from baseline in T2 lesion volume

End point title	Change from baseline in T2 lesion volume

End point description:

Magnetic resonance imaging (MRI) scans of the brain were performed every 12 months. MRI evaluation during the Core Part included the total volume of T2 lesions. Each MRI scan was reviewed by a local neurologist and by a central blinded MRI reading center.
The change from baseline in T2 lesion volume was analyzed using a mixed model for repeated measures (MMRM) with visit as a categorical factor and an unstructured covariance matrix and with adjustment for baseline covariates.

End point type	Secondary

End point timeframe:

Baseline, Month 12 and Month 24

End point values	Siponimod (BAF312)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	995	495		
Units: mm^3				
least squares mean (standard error)				
Month 12	204.9 (± 67.47)	818.0 (± 87.29)		
Month 24	162.9 (± 73.90)	940.4 (± 97.20)		
Average over Month 12 and Month 24	183.9 (± 66.33)	879.2 (± 85.43)		

Statistical analyses

Statistical analysis title	Month 12
Comparison groups	Siponimod (BAF312) v Placebo
Number of subjects included in analysis	1490
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-613.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-800.2
upper limit	-426
Variability estimate	Standard error of the mean
Dispersion value	95.39

Statistical analysis title	Average over Month 12 and Month 24
Comparison groups	Siponimod (BAF312) v Placebo
Number of subjects included in analysis	1490
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-695.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-877.3
upper limit	-513.3
Variability estimate	Standard error of the mean
Dispersion value	92.79

Statistical analysis title	Month 24
Comparison groups	Siponimod (BAF312) v Placebo
Number of subjects included in analysis	1490
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed model for repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-777.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-990.6
upper limit	-564.4
Variability estimate	Standard error of the mean
Dispersion value	108.62

Secondary: Percentage of participants with 6-month Confirmed Disability Progression (CDP) events as measured by the Expanded Disability Status Scale

(EDSS)

End point title	Percentage of participants with 6-month Confirmed Disability Progression (CDP) events as measured by the Expanded Disability Status Scale (EDSS)

End point description:

The EDSS uses an ordinal scale to assess neurologic impairment in multiple sclerosis (MS) based on a neurological examination. Scores in each of 7 functional systems (Visual, Brain Stem, Pyramidal, Cerebellar, Sensory, Bowel & Bladder, and Cerebral) and an ambulation score were combined to determine the EDSS steps, ranging from 0 (normal) to 10 (death due to MS).
6-month confirmed disability progression is defined as an increase of score of 1 point in patients with baseline score of 3.0 to 5.0 and 0.5 point increase with baseline score of 5.5 to 6.5 sustained for at least 6 months.
This outcome measure was analyzed using a Cox proportional hazards model.

End point type	Secondary

End point timeframe:

Baseline, every 3 months up to the maximum of approximately 3 years

End point values	Siponimod (BAF312)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1096	545		
Units: Percentage of participants				
number (not applicable)	19.9	25.5		

Statistical analyses

Statistical analysis title	6-month confirmed disability progression
Comparison groups	Siponimod (BAF312) v Placebo
Number of subjects included in analysis	1641
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0058
Method	Cox proportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	0.92

Secondary: Annualized relapse rate (ARR) for confirmed relapses

End point title	Annualized relapse rate (ARR) for confirmed relapses

End point description:

Multiple sclerosis (MS) relapse was defined as appearance of a new neurological abnormality or worsening of previously stable or improving pre-existing neurological abnormality, separated by at least 30 days from onset of a preceding clinical demyelinating event. Additionally, the abnormality had to be

present for at least 24 hours and occur in the absence of fever (<37.5°C) or known infection.
A confirmed MS relapse was defined as accompanied by a clinically-relevant change in the EDSS, as defined in the study protocol, performed by the Independent EDSS Rater.
ARR was defined as the average number of confirmed relapses per year.
ARR was analyzed using a negative binomial regression model.

End point type	Secondary

End point timeframe:

Up to maximum approximately 3 years

End point values	Siponimod (BAF312)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1099	546		
Units: Number of relapses				
arithmetic mean (confidence interval 95%)	0.071 (0.055 to 0.092)	0.160 (0.123 to 0.207)		

Statistical analyses

Statistical analysis title	ARR for confirmed relapses
Comparison groups	Siponimod (BAF312) v Placebo
Number of subjects included in analysis	1645
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Negative binomial regression model
Parameter estimate	ARR ratio
Point estimate	0.445
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.337
upper limit	0.587

Secondary: Percentage of participants with first relapse events as measured by time to first confirmed relapse

End point title	Percentage of participants with first relapse events as measured by time to first confirmed relapse

End point description:

Multiple sclerosis (MS) relapse was defined as appearance of a new neurological abnormality or worsening of previously stable or improving pre-existing neurological abnormality, separated by at least 30 days from onset of a preceding clinical demyelinating event. Additionally, the abnormality had to be present for at least 24 hours and occur in the absence of fever (<37.5°C) or known infection.
A confirmed MS relapse was defined as accompanied by a clinically-relevant change in the EDSS, as defined in the study protocol, performed by the Independent EDSS Rater.
Time to first relapse was defined as the time from Day 1 until the start of relapse symptoms. Patients without relapse were censored at the latest known date to be at risk.
This outcome measure was analyzed using a Cox proportional hazards model.

End point type	Secondary

End point timeframe:

Up to maximum approximately 3 years

End point values	Siponimod (BAF312)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1061	528		
Units: Percentage of participants				
number (not applicable)	10.7	18.9		

Statistical analyses

Statistical analysis title	Time to first relapse
Comparison groups	Siponimod (BAF312) v Placebo
Number of subjects included in analysis	1589
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cox proportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	0.7

Secondary: Percentage of patients with relapse (confirmed relapse and any relapse)

End point title	Percentage of patients with relapse (confirmed relapse and any relapse)

End point description:

Multiple sclerosis (MS) relapse was defined as appearance of a new neurological abnormality or worsening of previously stable or improving pre-existing neurological abnormality, separated by at least 30 days from onset of a preceding clinical demyelinating event. Additionally, the abnormality had to be present for at least 24 hours and occur in the absence of fever (<37.5°C) or known infection.
A confirmed MS relapse was defined as accompanied by a clinically-relevant change in the EDSS, as defined in the study protocol, performed by the Independent EDSS Rater.

End point type	Secondary

End point timeframe:

Up to maximum approximately 3 years

End point values	Siponimod (BAF312)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1099	546		
Units: Percentage of participants				
number (not applicable)				
Any relapse (confirmed or unconfirmed)	16.7	26.0		
Confirmed relapse	10.3	18.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in MSWS-12 converted score

End point title	Change from baseline in MSWS-12 converted score

End point description:

The Multiple Sclerosis Walking Scale (MSWS-12) version 2 is a patient-rated measure of walking consisting of 12 items. Walking limitations were reported by the patients using categories, generating a total transformed score ranging from 0-100. Higher scores reflected greater impairment.
The change from baseline in MSWS-12 converted score was analyzed using a repeated measures model.

End point type	Secondary

End point timeframe:

Baseline, Month 12 and Month 24

End point values	Siponimod (BAF312)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1022	516		
Units: score on a scale				
least squares mean (standard error)				
Month 12	1.53 (± 0.678)	3.36 (± 0.908)		
Month 24	4.16 (± 0.848)	5.38 (± 1.167)		

Statistical analyses

Statistical analysis title	Month 24
Comparison groups	Siponimod (BAF312) v Placebo
Number of subjects included in analysis	1538
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3671
Method	Repeated measures model
Parameter estimate	Mean difference (final values)
Point estimate	-1.23

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.89
upper limit	1.44
Variability estimate	Standard error of the mean
Dispersion value	1.359

Statistical analysis title	Month 12
Comparison groups	Siponimod (BAF312) v Placebo
Number of subjects included in analysis	1538
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0764
Method	Repeated measures model
Parameter estimate	Mean difference (final values)
Point estimate	-1.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.85
upper limit	0.19
Variability estimate	Standard error of the mean
Dispersion value	1.03

Secondary: Number of T1 Gd-enhancing lesions per patient per scan

End point title	Number of T1 Gd-enhancing lesions per patient per scan

End point description:

Magnetic resonance imaging (MRI) scans of the brain were performed every 12 months. MRI evaluation during the Core Part included the number of T1 gadolinium (Gd)-enhancing lesions. Each MRI scan was reviewed by a local neurologist and by a central blinded MRI reading center.
The number of T1 Gd-enhancing lesions per patient per scan was analyzed using a negative binomial regression model.

End point type	Secondary

End point timeframe:

Baseline, Month 12 and Month 24

End point values	Siponimod (BAF312)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	996	496		
Units: Number of T1 Gd-enhancing lesions				
least squares mean (confidence interval 95%)				

Month 12	0.080 (0.058 to 0.111)	0.640 (0.488 to 0.839)		
Month 24	0.074 (0.040 to 0.138)	0.418 (0.288 to 0.607)		

Statistical analyses

Statistical analysis title	Month 24
Comparison groups	Siponimod (BAF312) v Placebo
Number of subjects included in analysis	1492
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Negative binomial regression model
Parameter estimate	Rate ratio
Point estimate	0.178
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.087
upper limit	0.362

Statistical analysis title	Month 12
Comparison groups	Siponimod (BAF312) v Placebo
Number of subjects included in analysis	1492
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Negative binomial regression model
Parameter estimate	Rate ratio
Point estimate	0.126
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.083
upper limit	0.191

Secondary: Number of new or enlarging T2 lesions per patient per year

End point title	Number of new or enlarging T2 lesions per patient per year

End point description:

Magnetic resonance imaging (MRI) scans of the brain were performed every 12 months. MRI evaluation during the Core Part included the number of new or enlarging T2 lesions. Each MRI scan was reviewed by a local neurologist and by a central blinded MRI reading center.
The number of new or enlarging T2 lesions compared to previous scan was analyzed using a repeated measures negative binomial regression model.

End point type	Secondary

End point timeframe: Baseline, Month 12 and Month 24

End point values	Siponimod (BAF312)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	997	496		
Units: Number of T2 lesions				
least squares mean (confidence interval 95%)				
Month 12	1.003 (0.858 to 1.172)	3.776 (3.148 to 4.528)		
Month 24	0.489 (0.371 to 0.644)	3.437 (2.800 to 4.220)		

Statistical analyses

Statistical analysis title	Month 24
Comparison groups	Siponimod (BAF312) v Placebo
Number of subjects included in analysis	1493
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Regression model
Parameter estimate	Rate ratio
Point estimate	0.142
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.103
upper limit	0.196

Statistical analysis title	Month 12
Comparison groups	Siponimod (BAF312) v Placebo
Number of subjects included in analysis	1493
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Regression model
Parameter estimate	Rate ratio
Point estimate	0.266

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.215
upper limit	0.328

Secondary: Percent brain volume change (PBVC) relative to baseline

End point title	Percent brain volume change (PBVC) relative to baseline

End point description:

Magnetic resonance imaging (MRI) scans of the brain were performed every 12 months. MRI evaluation during the Core Part included the percentage change in brain volume. Each MRI scan was reviewed by a local neurologist and by a central blinded MRI reading center.
PBVC relative to baseline was analyzed using a repeated measures model (for normally distributed data) with visit as a categorical factor.

End point type	Secondary

End point timeframe:

Baseline, Month 12 and Month 24

End point values	Siponimod (BAF312)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	894	436		
Units: % change from baseline in brain volume				
least squares mean (standard error)				
Month 12	-0.283 (± 0.0264)	-0.458 (± 0.0341)		
Month 24	-0.711 (± 0.0356)	-0.839 (± 0.0476)		

Statistical analyses

Statistical analysis title	Month 24
Comparison groups	Siponimod (BAF312) v Placebo
Number of subjects included in analysis	1330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0196
Method	Repeated measures model
Parameter estimate	Mean difference (final values)
Point estimate	0.128
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.021
upper limit	0.236

Variability estimate	Standard error of the mean
Dispersion value	0.0549

Statistical analysis title	Month 12
Comparison groups	Siponimod (BAF312) v Placebo
Number of subjects included in analysis	1330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Repeated measures model
Parameter estimate	Mean difference (final values)
Point estimate	0.175
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.103
upper limit	0.247
Variability estimate	Standard error of the mean
Dispersion value	0.0367

Secondary: Number of participants with 3-month CDP events as measured by EDSS in the subgroup of SPMS patients with/without superimposed relapses

End point title	Number of participants with 3-month CDP events as measured by EDSS in the subgroup of SPMS patients with/without superimposed relapses

End point description:

The Expanded Disability Status Scale (EDSS) assesses neurologic impairment in multiple sclerosis (MS). EDSS scale ranges from 0 (normal) to 10 (death due to MS). Confirmed disability is defined as an increase of score of 1 point in patients with baseline score of 3.0 to 5.0 and 0.5 point increase with baseline score of 5.5 to 6.5.
The definition of 3-month confirmed disability progression (CDP) was an increase from baseline in EDSS as defined before sustained for at least 3 months.
The following secondary progressive multiple sclerosis (SPMS) groups were defined for the analysis of this endpoint:
• Without superimposed relapses in the 2 years prior to study start (baseline definition)
• With superimposed relapses in the 2 years prior to study start (baseline definition)
• Without superimposed relapses during the Core Part of study (post-treatment)
• With superimposed relapses during the Core Part of study (post-treatment)
Data was analyzed using a Cox proportional hazard model.

End point type	Secondary

End point timeframe:

Baseline, every 3 months up to the maximum of approximately 3 years

End point values	Siponimod (BAF312)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1099	546		
Units: Participants				
W/O superimposed relapses at baseline (n=708, 343)	190	101		
W/ superimposed relapses at baseline (n=388, 202)	98	72		
W/O superimposed relapses post-treat. (n=986, 444)	237	122		
W/ superimposed relapses post-treat. (n=113, 102)	51	51		

Statistical analyses

Statistical analysis title	Without superimposed relapses at baseline
Comparison groups	Siponimod (BAF312) v Placebo
Number of subjects included in analysis	1645
Analysis specification	Pre-specified
Analysis type	superiority
Method	Cox proportional hazard model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	1.11

Statistical analysis title	With superimposed relapses post-treatment
Comparison groups	Siponimod (BAF312) v Placebo
Number of subjects included in analysis	1645
Analysis specification	Pre-specified
Analysis type	superiority
Method	Cox proportional hazard model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	1.19

Statistical analysis title	Without superimposed relapses post-treatment
Comparison groups	Siponimod (BAF312) v Placebo

Number of subjects included in analysis	1645
Analysis specification	Pre-specified
Analysis type	superiority
Method	Cox proportional hazard model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.06

Statistical analysis title	With superimposed relapses at baseline
Comparison groups	Siponimod (BAF312) v Placebo
Number of subjects included in analysis	1645
Analysis specification	Pre-specified
Analysis type	superiority
Method	Cox proportional hazard model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	0.91

Secondary: Number of participants with 3-month CDP events as measured by EDSS in the subgroup of rapidly and not rapidly evolving patients

End point title	Number of participants with 3-month CDP events as measured by EDSS in the subgroup of rapidly and not rapidly evolving patients

End point description:

The Expanded Disability Status Scale (EDSS) assesses neurologic impairment in multiple sclerosis (MS). EDSS scale ranges from 0 (normal) to 10 (death due to MS). Confirmed disability is defined as an increase of score of 1 point in patients with baseline score of 3.0 to 5.0 and 0.5 point increase with baseline score of 5.5 to 6.5.
The definition of 3-month confirmed disability progression (CDP) was an increase from baseline in EDSS as defined before sustained for at least 3 months.
Rapidly evolving patients are defined as subjects with 1.5 or greater EDSS change in the 2 years prior to or at study start and disability progression in the 2 years prior to study start was not adjudicated.
Data was analyzed using a Cox proportional hazard model.

End point type	Secondary

End point timeframe:

Baseline, every 3 months up to the maximum of approximately 3 years

End point values	Siponimod (BAF312)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1099	546		
Units: Participants				
Rapidly evolving patients (n=264, 145)	82	60		
Not rapidly evolving patients (n=835, 401)	206	113		

Statistical analyses

Statistical analysis title	Rapidly evolving patients
Comparison groups	Siponimod (BAF312) v Placebo
Number of subjects included in analysis	1645
Analysis specification	Pre-specified
Analysis type	superiority
Method	Cox proportional hazard model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	0.91

Statistical analysis title	Not rapidly evolving patients
Comparison groups	Siponimod (BAF312) v Placebo
Number of subjects included in analysis	1645
Analysis specification	Pre-specified
Analysis type	superiority
Method	Cox proportional hazard model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.09

Secondary: Number of participants with 3-month CDP events as measured by EDSS in the subgroup of patients with and without moderate/severe disease course

End point title	Number of participants with 3-month CDP events as measured by EDSS in the subgroup of patients with and without moderate/severe disease course

End point description:

The Expanded Disability Status Scale (EDSS) assesses neurologic impairment in multiple sclerosis (MS). EDSS scale ranges from 0 (normal) to 10 (death due to MS). Confirmed disability is defined as an increase of score of 1 point in patients with baseline score of 3.0 to 5.0 and 0.5 point increase with baseline score of 5.5 to 6.5.
The definition of 3-month confirmed disability progression (CDP) was an increase from baseline in EDSS as defined before sustained for at least 3 months.
Moderate or severe course of disease is defined as global Multiple Sclerosis Severity Score (MSSS) of 4 or more at baseline.
Data was analyzed using a Cox proportional hazard model.

End point type	Secondary

End point timeframe:

Baseline, every 3 months up to the maximum of approximately 3 years

End point values	Siponimod (BAF312)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1099	546		
Units: Participants				
With moderate or severe disease (n=904, 459)	232	141		
Without moderate or severe disease (n=195, 87)	56	32		

Statistical analyses

Statistical analysis title	Without moderate or severe course of disease
Comparison groups	Siponimod (BAF312) v Placebo
Number of subjects included in analysis	1645
Analysis specification	Pre-specified
Analysis type	superiority
Method	Cox proportional hazard model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	1.13

Statistical analysis title	With moderate or severe course of disease
Comparison groups	Siponimod (BAF312) v Placebo

Number of subjects included in analysis	1645
Analysis specification	Pre-specified
Analysis type	superiority
Method	Cox proportional hazard model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	0.99

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Core Part: from first dose of double-blind study treatment until end of Core Part (up to approximately 3 years).
Core and Extension: from first dose of siponimod until end of study (up to approximately 10 years).

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	26.0

Reporting groups

Reporting group title	Core-BAF312

Reporting group description:

Participants who were randomized to siponimod (BAF312) during the Core Part

Reporting group title	All BAF312

Reporting group description:

All participants who received at least one dose of siponimod (BAF312) during the Core Part and/or the Extension Part

Reporting group title	Core-Placebo

Reporting group description:

Participants who were randomized to placebo during the Core Part

Serious adverse events	Core-BAF312	All BAF312	Core-Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	196 / 1099 (17.83%)	610 / 1517 (40.21%)	83 / 546 (15.20%)
number of deaths (all causes)	4	33	4
number of deaths resulting from adverse events	2	7	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 1099 (0.09%)	7 / 1517 (0.46%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	1 / 1	3 / 7	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain neoplasm malignant			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Bowen's disease			

subjects affected / exposed	1 / 1099 (0.09%)	18 / 1517 (1.19%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 1	14 / 19	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder cancer			
subjects affected / exposed	0 / 1099 (0.00%)	0 / 1517 (0.00%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign renal neoplasm			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Benign neoplasm of thyroid gland			
subjects affected / exposed	1 / 1099 (0.09%)	2 / 1517 (0.13%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Astrocytoma			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Basal cell carcinoma			
subjects affected / exposed	11 / 1099 (1.00%)	68 / 1517 (4.48%)	7 / 546 (1.28%)
occurrences causally related to treatment / all	5 / 12	68 / 102	6 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intraductal proliferative breast lesion			
subjects affected / exposed	0 / 1099 (0.00%)	3 / 1517 (0.20%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glioma			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal melanoma			

subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	1 / 1	0 / 0
Gastric cancer			
subjects affected / exposed	0 / 1099 (0.00%)	0 / 1517 (0.00%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Endometrial cancer			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Dysplastic naevus			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Diffuse large B-cell lymphoma			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Colorectal cancer			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Colon cancer stage IV			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	1 / 1	0 / 0
Colon cancer metastatic			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Colon cancer			

subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Cervix carcinoma			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Central nervous system lymphoma			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 1099 (0.00%)	4 / 1517 (0.26%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Keratoacanthoma			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Lip squamous cell carcinoma			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Skin cancer			
subjects affected / exposed	0 / 1099 (0.00%)	2 / 1517 (0.13%)	0 / 546 (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
Seminoma			
subjects affected / exposed	2 / 1099 (0.18%)	2 / 1517 (0.13%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal oncocytoma			

subjects affected / exposed	0 / 1099 (0.00%)	0 / 1517 (0.00%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	0 / 1099 (0.00%)	3 / 1517 (0.20%)	2 / 546 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-small cell lung cancer metastatic			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Neurofibroma			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Meningioma			
subjects affected / exposed	0 / 1099 (0.00%)	2 / 1517 (0.13%)	0 / 546 (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
Melanocytic naevus			
subjects affected / exposed	1 / 1099 (0.09%)	4 / 1517 (0.26%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma in situ			
subjects affected / exposed	2 / 1099 (0.18%)	2 / 1517 (0.13%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma			
subjects affected / exposed	0 / 1099 (0.00%)	6 / 1517 (0.40%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 0	5 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm			

subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Lung adenocarcinoma			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Vulval cancer stage 0			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Uterine leiomyoma			
subjects affected / exposed	1 / 1099 (0.09%)	6 / 1517 (0.40%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 6	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Testis cancer			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Squamous cell carcinoma of the vagina			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 1099 (0.00%)	10 / 1517 (0.66%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 0	9 / 10	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			
subjects affected / exposed	1 / 1099 (0.09%)	8 / 1517 (0.53%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 1	3 / 9	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small cell lung cancer metastatic			

subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Superficial spreading melanoma stage unspecified			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Hypertensive emergency			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Hypertension			
subjects affected / exposed	1 / 1099 (0.09%)	2 / 1517 (0.13%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Essential hypertension			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Deep vein thrombosis			
subjects affected / exposed	1 / 1099 (0.09%)	5 / 1517 (0.33%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Circulatory collapse			

subjects affected / exposed	0 / 1099 (0.00%)	2 / 1517 (0.13%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery occlusion			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Orthostatic hypotension			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Internal haemorrhage			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Venous thrombosis limb			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Vasculitis			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	1 / 1099 (0.09%)	2 / 1517 (0.13%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 1099 (0.18%)	4 / 1517 (0.26%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Accidental death			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Chills			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Disease progression			
subjects affected / exposed	0 / 1099 (0.00%)	2 / 1517 (0.13%)	0 / 546 (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
Fatigue			
subjects affected / exposed	1 / 1099 (0.09%)	3 / 1517 (0.20%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gait disturbance			
subjects affected / exposed	1 / 1099 (0.09%)	3 / 1517 (0.20%)	3 / 546 (0.55%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 1099 (0.00%)	2 / 1517 (0.13%)	0 / 546 (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
Granuloma			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Oedema peripheral			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impaired healing			

subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Influenza like illness			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Malaise			
subjects affected / exposed	0 / 1099 (0.00%)	2 / 1517 (0.13%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Hyperpyrexia			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Pain			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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	2 / 1099 (0.18%)	11 / 1517 (0.73%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 2	3 / 11	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden cardiac death			

subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Sudden death			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Immune reconstitution inflammatory syndrome			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Social circumstances			
Immobile			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Walking disability			
subjects affected / exposed	0 / 1099 (0.00%)	0 / 1517 (0.00%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Cervical polyp			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Cervical dysplasia			

subjects affected / exposed	0 / 1099 (0.00%)	0 / 1517 (0.00%)	1 / 546 (0.18%)
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 / 1099 (0.00%)	2 / 1517 (0.13%)	0 / 546 (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
Endometrial hyperplasia			
subjects affected / exposed	0 / 1099 (0.00%)	2 / 1517 (0.13%)	0 / 546 (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
Heavy menstrual bleeding			
subjects affected / exposed	2 / 1099 (0.18%)	3 / 1517 (0.20%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intermenstrual bleeding			
subjects affected / exposed	2 / 1099 (0.18%)	2 / 1517 (0.13%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	1 / 2	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cyst			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Ovarian disorder			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Prostatitis			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Testicular atrophy			

subjects affected / exposed	0 / 1099 (0.00%)	0 / 1517 (0.00%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vaginal haemorrhage			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 1099 (0.00%)	3 / 1517 (0.20%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Asthma			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 1099 (0.00%)	3 / 1517 (0.20%)	0 / 546 (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
Dyspnoea			
subjects affected / exposed	0 / 1099 (0.00%)	2 / 1517 (0.13%)	0 / 546 (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
Hyperventilation			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Laryngeal stenosis			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Pulmonary embolism			

subjects affected / exposed	1 / 1099 (0.09%)	8 / 1517 (0.53%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 8	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 3	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 1099 (0.00%)	2 / 1517 (0.13%)	0 / 546 (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
Nasal polyps			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Pulmonary hypertension			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Pulmonary mass			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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 depression			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Respiratory failure			
subjects affected / exposed	0 / 1099 (0.00%)	5 / 1517 (0.33%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Respiratory paralysis			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Sleep apnoea syndrome			

subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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 disorder			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Psychiatric disorders			
Acute psychosis			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Euphoric mood			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Drug abuse			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Disorientation			
subjects affected / exposed	0 / 1099 (0.00%)	3 / 1517 (0.20%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Depressive symptom			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Depression suicidal			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Depression			

subjects affected / exposed	3 / 1099 (0.27%)	3 / 1517 (0.20%)	2 / 546 (0.37%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Hallucination			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Confusional state			
subjects affected / exposed	0 / 1099 (0.00%)	4 / 1517 (0.26%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Completed suicide			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Anxiety disorder due to a general medical condition			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Anxiety			
subjects affected / exposed	1 / 1099 (0.09%)	2 / 1517 (0.13%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adjustment disorder			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Depressed mood			
subjects affected / exposed	1 / 1099 (0.09%)	0 / 1517 (0.00%)	0 / 546 (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
Suicide attempt			

subjects affected / exposed	4 / 1099 (0.36%)	8 / 1517 (0.53%)	3 / 546 (0.55%)
occurrences causally related to treatment / all	0 / 4	0 / 9	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	3 / 1099 (0.27%)	8 / 1517 (0.53%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 3	2 / 8	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal behaviour			
subjects affected / exposed	3 / 1099 (0.27%)	4 / 1517 (0.26%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic disorder			
subjects affected / exposed	1 / 1099 (0.09%)	2 / 1517 (0.13%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Panic attack			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mixed anxiety and depressive disorder			
subjects affected / exposed	2 / 1099 (0.18%)	2 / 1517 (0.13%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Mania			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Major depression			

subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Insomnia			
subjects affected / exposed	0 / 1099 (0.00%)	2 / 1517 (0.13%)	0 / 546 (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
Product issues			
Device breakage			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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			
Bile duct stone			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Biliary colic			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Cholecystitis			
subjects affected / exposed	1 / 1099 (0.09%)	4 / 1517 (0.26%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	1 / 1099 (0.09%)	3 / 1517 (0.20%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	1 / 1099 (0.09%)	5 / 1517 (0.33%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			

subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Hepatic function abnormal			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Hepatic steatosis			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Hepatitis acute			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Hepatotoxicity			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Liver disorder			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Non-alcoholic steatohepatitis			
subjects affected / exposed	0 / 1099 (0.00%)	0 / 1517 (0.00%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	10 / 1099 (0.91%)	19 / 1517 (1.25%)	2 / 546 (0.37%)
occurrences causally related to treatment / all	10 / 11	16 / 22	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			

subjects affected / exposed	5 / 1099 (0.45%)	9 / 1517 (0.59%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	4 / 5	7 / 10	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	2 / 1099 (0.18%)	3 / 1517 (0.20%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	2 / 2	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood glucose increased			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Blood pressure decreased			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
CD4 lymphocytes decreased			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
CD8 lymphocytes decreased			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Walking distance test abnormal			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Troponin increased			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Pulmonary function test decreased			

subjects affected / exposed	1 / 1099 (0.09%)	2 / 1517 (0.13%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Magnetic resonance imaging abnormal			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Lung diffusion test decreased			
subjects affected / exposed	1 / 1099 (0.09%)	2 / 1517 (0.13%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver function test increased			
subjects affected / exposed	0 / 1099 (0.00%)	2 / 1517 (0.13%)	0 / 546 (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
Liver function test abnormal			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased			
subjects affected / exposed	1 / 1099 (0.09%)	4 / 1517 (0.26%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	1 / 1	3 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme abnormal			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Heart rate decreased			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Columbia suicide severity rating scale abnormal			

subjects affected / exposed	2 / 1099 (0.18%)	2 / 1517 (0.13%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 1099 (0.09%)	3 / 1517 (0.20%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Concussion			
subjects affected / exposed	5 / 1099 (0.45%)	8 / 1517 (0.53%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 9	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clavicle fracture			
subjects affected / exposed	2 / 1099 (0.18%)	2 / 1517 (0.13%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical vertebral fracture			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Bursa injury			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Burns third degree			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Brain contusion			

subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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 contusion			
subjects affected / exposed	0 / 1099 (0.00%)	2 / 1517 (0.13%)	0 / 546 (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
Ankle fracture			
subjects affected / exposed	2 / 1099 (0.18%)	8 / 1517 (0.53%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 8	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Accidental overdose			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injection related reaction			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Humerus fracture			
subjects affected / exposed	0 / 1099 (0.00%)	4 / 1517 (0.26%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 1099 (0.00%)	5 / 1517 (0.33%)	2 / 546 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 5	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	0 / 1099 (0.00%)	2 / 1517 (0.13%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture displacement			

subjects affected / exposed	1 / 1099 (0.09%)	2 / 1517 (0.13%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot fracture			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury corneal			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Femur fracture			
subjects affected / exposed	0 / 1099 (0.00%)	3 / 1517 (0.20%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	3 / 1099 (0.27%)	13 / 1517 (0.86%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 3	0 / 15	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	2 / 1099 (0.18%)	11 / 1517 (0.73%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 13	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Eye contusion			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Craniocerebral injury			
subjects affected / exposed	0 / 1099 (0.00%)	2 / 1517 (0.13%)	0 / 546 (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
Fibula fracture			

subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Intentional overdose			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Reactive gastropathy			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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	1 / 1099 (0.09%)	3 / 1517 (0.20%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural pain			
subjects affected / exposed	0 / 1099 (0.00%)	2 / 1517 (0.13%)	0 / 546 (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
Post-traumatic pain			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Post procedural haemorrhage			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Post procedural haematoma			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Nerve root injury cervical			

subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Meniscus injury			
subjects affected / exposed	0 / 1099 (0.00%)	2 / 1517 (0.13%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Maisonneuve fracture			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Lumbar vertebral fracture			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Lower limb fracture			
subjects affected / exposed	0 / 1099 (0.00%)	2 / 1517 (0.13%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament injury			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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 dislocation			
subjects affected / exposed	0 / 1099 (0.00%)	3 / 1517 (0.20%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon rupture			
subjects affected / exposed	0 / 1099 (0.00%)	0 / 1517 (0.00%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			

subjects affected / exposed	1 / 1099 (0.09%)	6 / 1517 (0.40%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haematoma			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Stress fracture			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Sternal fracture			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Splenic rupture			
subjects affected / exposed	1 / 1099 (0.09%)	2 / 1517 (0.13%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thermal burn			
subjects affected / exposed	1 / 1099 (0.09%)	2 / 1517 (0.13%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	1 / 1099 (0.09%)	2 / 1517 (0.13%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin laceration			
subjects affected / exposed	4 / 1099 (0.36%)	8 / 1517 (0.53%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 9	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin abrasion			

subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Shoulder fracture			
subjects affected / exposed	0 / 1099 (0.00%)	2 / 1517 (0.13%)	0 / 546 (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
Road traffic accident			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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 / 1099 (0.09%)	4 / 1517 (0.26%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic injury			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Tibia fracture			
subjects affected / exposed	0 / 1099 (0.00%)	3 / 1517 (0.20%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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 fracture			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Traumatic haemorrhage			

subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Traumatic haemothorax			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Traumatic liver injury			
subjects affected / exposed	1 / 1099 (0.09%)	2 / 1517 (0.13%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			
subjects affected / exposed	0 / 1099 (0.00%)	2 / 1517 (0.13%)	0 / 546 (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
Wound			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Wrist fracture			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Congenital, familial and genetic disorders			
Brugada syndrome			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Corneal dystrophy			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Malformation venous			

subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	1 / 1099 (0.09%)	3 / 1517 (0.20%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Angina pectoris			
subjects affected / exposed	1 / 1099 (0.09%)	3 / 1517 (0.20%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	1 / 1	1 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Acute coronary syndrome			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Atrioventricular block second degree			
subjects affected / exposed	2 / 1099 (0.18%)	2 / 1517 (0.13%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	4 / 4	4 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	3 / 1099 (0.27%)	4 / 1517 (0.26%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	3 / 3	5 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			

subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Myocarditis			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Cardio-respiratory arrest			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Coronary artery disease			
subjects affected / exposed	1 / 1099 (0.09%)	2 / 1517 (0.13%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 1099 (0.00%)	2 / 1517 (0.13%)	0 / 546 (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
Myocardial ischaemia			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Cardiac failure acute			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Palpitations			

subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Supraventricular extrasystoles			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Supraventricular tachycardia			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachyarrhythmia			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Tachycardia			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Ventricular tachycardia			
subjects affected / exposed	0 / 1099 (0.00%)	2 / 1517 (0.13%)	0 / 546 (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
Nervous system disorders			
Amyotrophic lateral sclerosis			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Allodynia			
subjects affected / exposed	0 / 1099 (0.00%)	0 / 1517 (0.00%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ataxia			

subjects affected / exposed	1 / 1099 (0.09%)	2 / 1517 (0.13%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aphasia			
subjects affected / exposed	1 / 1099 (0.09%)	2 / 1517 (0.13%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	2 / 1099 (0.18%)	7 / 1517 (0.46%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 2	0 / 7	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clonic convulsion			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Cognitive disorder			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Disturbance in attention			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Dizziness			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Autoimmune demyelinating disease			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Brain injury			

subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Brain stem infarction			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Central nervous system lesion			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Cerebral haematoma			
subjects affected / exposed	0 / 1099 (0.00%)	2 / 1517 (0.13%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	0 / 1099 (0.00%)	2 / 1517 (0.13%)	0 / 546 (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
Cerebral infarction			
subjects affected / exposed	0 / 1099 (0.00%)	3 / 1517 (0.20%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral venous sinus thrombosis			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Dysaesthesia			
subjects affected / exposed	0 / 1099 (0.00%)	0 / 1517 (0.00%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysarthria			

subjects affected / exposed	0 / 1099 (0.00%)	3 / 1517 (0.20%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	1 / 1099 (0.09%)	4 / 1517 (0.26%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial aneurysm			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intention tremor			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Hypokinesia			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Hypoaesthesia			
subjects affected / exposed	0 / 1099 (0.00%)	0 / 1517 (0.00%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	3 / 1099 (0.27%)	4 / 1517 (0.26%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head titubation			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Haemorrhagic stroke			

subjects affected / exposed	0 / 1099 (0.00%)	0 / 1517 (0.00%)	1 / 546 (0.18%)
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	1 / 1099 (0.09%)	3 / 1517 (0.20%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile infection-related epilepsy syndrome			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Facial paresis			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Epilepsy			
subjects affected / exposed	5 / 1099 (0.45%)	22 / 1517 (1.45%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 9	0 / 29	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple sclerosis relapse			
subjects affected / exposed	2 / 1099 (0.18%)	7 / 1517 (0.46%)	7 / 546 (1.28%)
occurrences causally related to treatment / all	1 / 2	1 / 7	1 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple sclerosis pseudo relapse			
subjects affected / exposed	0 / 1099 (0.00%)	3 / 1517 (0.20%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple sclerosis			
subjects affected / exposed	2 / 1099 (0.18%)	17 / 1517 (1.12%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	1 / 2	2 / 19	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Motor dysfunction			

subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Migraine with aura			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Optic neuritis			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Meralgia paraesthetica			
subjects affected / exposed	0 / 1099 (0.00%)	0 / 1517 (0.00%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Lacunar stroke			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Lacunar infarction			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Muscle spasticity			
subjects affected / exposed	2 / 1099 (0.18%)	9 / 1517 (0.59%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	1 / 3	1 / 12	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Migraine			

subjects affected / exposed	0 / 1099 (0.00%)	2 / 1517 (0.13%)	0 / 546 (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
Paraparesis			
subjects affected / exposed	0 / 1099 (0.00%)	2 / 1517 (0.13%)	3 / 546 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Secondary progressive multiple sclerosis			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Radiculopathy			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Quadriplegia			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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 / 1099 (0.00%)	2 / 1517 (0.13%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Putamen haemorrhage			
subjects affected / exposed	0 / 1099 (0.00%)	0 / 1517 (0.00%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudobulbar palsy			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Progressive multiple sclerosis			

subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Presyncope			
subjects affected / exposed	0 / 1099 (0.00%)	2 / 1517 (0.13%)	0 / 546 (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
Postictal paralysis			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Post herpetic neuralgia			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Polyneuropathy			
subjects affected / exposed	1 / 1099 (0.09%)	2 / 1517 (0.13%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Partial seizures			
subjects affected / exposed	2 / 1099 (0.18%)	6 / 1517 (0.40%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 7	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parkinson's disease			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Uhthoff's phenomenon			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Trigeminal neuralgia			

subjects affected / exposed	3 / 1099 (0.27%)	12 / 1517 (0.79%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 4	1 / 14	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tremor			
subjects affected / exposed	0 / 1099 (0.00%)	0 / 1517 (0.00%)	1 / 546 (0.18%)
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	1 / 1099 (0.09%)	6 / 1517 (0.40%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 1	1 / 7	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	4 / 1099 (0.36%)	6 / 1517 (0.40%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	1 / 4	2 / 7	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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 migrainosus			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Status epilepticus			
subjects affected / exposed	0 / 1099 (0.00%)	4 / 1517 (0.26%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	4 / 1099 (0.36%)	7 / 1517 (0.46%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 13	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural hygroma			

subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Amnestic disorder			
subjects affected / exposed	0 / 1099 (0.00%)	0 / 1517 (0.00%)	1 / 546 (0.18%)
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			
subjects affected / exposed	0 / 1099 (0.00%)	4 / 1517 (0.26%)	2 / 546 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 4	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphocytic infiltration			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Leukopenia			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Hypochromic anaemia			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Lymphopenia			
subjects affected / exposed	0 / 1099 (0.00%)	4 / 1517 (0.26%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 0	4 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Thrombocytopenia			

subjects affected / exposed	1 / 1099 (0.09%)	2 / 1517 (0.13%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 1099 (0.00%)	0 / 1517 (0.00%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deafness transitory			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Hypoacusis			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Eye disorders			
Blindness			
subjects affected / exposed	1 / 1099 (0.09%)	2 / 1517 (0.13%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract			
subjects affected / exposed	0 / 1099 (0.00%)	2 / 1517 (0.13%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diplopia			
subjects affected / exposed	0 / 1099 (0.00%)	0 / 1517 (0.00%)	1 / 546 (0.18%)
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 hole			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Macular oedema			

subjects affected / exposed	3 / 1099 (0.27%)	6 / 1517 (0.40%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	2 / 3	4 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Photophobia			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Retinal detachment			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinoschisis			
subjects affected / exposed	0 / 1099 (0.00%)	0 / 1517 (0.00%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye haemorrhage			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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 / 1099 (0.00%)	2 / 1517 (0.13%)	0 / 546 (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
Abdominal pain upper			
subjects affected / exposed	0 / 1099 (0.00%)	0 / 1517 (0.00%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acquired oesophageal web			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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 fissure			

subjects affected / exposed	0 / 1099 (0.00%)	0 / 1517 (0.00%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal haemorrhage			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	2 / 1099 (0.18%)	6 / 1517 (0.40%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 2	0 / 7	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 1099 (0.09%)	2 / 1517 (0.13%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis erosive			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Dysphagia			
subjects affected / exposed	0 / 1099 (0.00%)	3 / 1517 (0.20%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Faecaloma			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Gastric haemorrhage			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Gastric perforation			

subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Gastric ulcer perforation			
subjects affected / exposed	0 / 1099 (0.00%)	0 / 1517 (0.00%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 1099 (0.00%)	2 / 1517 (0.13%)	0 / 546 (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
Duodenal ulcer			
subjects affected / exposed	0 / 1099 (0.00%)	0 / 1517 (0.00%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Ileus			
subjects affected / exposed	0 / 1099 (0.00%)	2 / 1517 (0.13%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Ileus paralytic			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Impaired gastric emptying			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Incarcerated inguinal hernia			

subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Haematemesis			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Intestinal obstruction			
subjects affected / exposed	1 / 1099 (0.09%)	2 / 1517 (0.13%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Oesophagitis			
subjects affected / exposed	0 / 1099 (0.00%)	0 / 1517 (0.00%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal inflammation			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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 / 1099 (0.09%)	7 / 1517 (0.46%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 7	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			

subjects affected / exposed	0 / 1099 (0.00%)	2 / 1517 (0.13%)	0 / 546 (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
Pancreatitis acute			
subjects affected / exposed	0 / 1099 (0.00%)	0 / 1517 (0.00%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritoneal adhesions			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Rectal haemorrhage			
subjects affected / exposed	0 / 1099 (0.00%)	2 / 1517 (0.13%)	0 / 546 (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
Rectal polyp			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Rectal prolapse			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Subileus			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Toothache			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Umbilical hernia, obstructive			

subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Volvulus			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Vomiting			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Small intestinal obstruction			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	1 / 1099 (0.09%)	4 / 1517 (0.26%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Actinic elastosis			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Actinic keratosis			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Eczema			

subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Dermal cyst			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Rash papular			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Renal and urinary disorders			
Bladder dysfunction			
subjects affected / exposed	2 / 1099 (0.18%)	3 / 1517 (0.20%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			
subjects affected / exposed	1 / 1099 (0.09%)	5 / 1517 (0.33%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder hypertrophy			
subjects affected / exposed	0 / 1099 (0.00%)	2 / 1517 (0.13%)	0 / 546 (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
Obstructive nephropathy			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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	1 / 1099 (0.09%)	2 / 1517 (0.13%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrotic syndrome			

subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	1 / 1099 (0.09%)	4 / 1517 (0.26%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephritis			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Bladder leukoplakia			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Haematuria			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Dysuria			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Cystitis noninfective			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Calculus urinary			
subjects affected / exposed	0 / 1099 (0.00%)	2 / 1517 (0.13%)	0 / 546 (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
Calculus bladder			

subjects affected / exposed	1 / 1099 (0.09%)	2 / 1517 (0.13%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	2 / 1099 (0.18%)	2 / 1517 (0.13%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	1 / 2	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract obstruction			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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	3 / 1099 (0.27%)	9 / 1517 (0.59%)	2 / 546 (0.37%)
occurrences causally related to treatment / all	0 / 3	0 / 9	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary incontinence			
subjects affected / exposed	2 / 1099 (0.18%)	3 / 1517 (0.20%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urge incontinence			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Urethral stenosis			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureterolithiasis			
subjects affected / exposed	1 / 1099 (0.09%)	3 / 1517 (0.20%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Single functional kidney			

subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Renal cyst			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Renal colic			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Graves' disease			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Hyperthyroidism			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 1099 (0.09%)	0 / 1517 (0.00%)	0 / 546 (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
Arthralgia			
subjects affected / exposed	1 / 1099 (0.09%)	3 / 1517 (0.20%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Back pain			
subjects affected / exposed	1 / 1099 (0.09%)	4 / 1517 (0.26%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bursitis			
subjects affected / exposed	1 / 1099 (0.09%)	3 / 1517 (0.20%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoroacetabular impingement			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Foot deformity			
subjects affected / exposed	1 / 1099 (0.09%)	2 / 1517 (0.13%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	1 / 1099 (0.09%)	2 / 1517 (0.13%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament disorder			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Lumbar spinal stenosis			
subjects affected / exposed	1 / 1099 (0.09%)	2 / 1517 (0.13%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle spasms			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Muscular weakness			

subjects affected / exposed	3 / 1099 (0.27%)	7 / 1517 (0.46%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 6	1 / 10	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 1099 (0.00%)	2 / 1517 (0.13%)	0 / 546 (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
Musculoskeletal pain			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Musculoskeletal stiffness			
subjects affected / exposed	0 / 1099 (0.00%)	0 / 1517 (0.00%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neck pain			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Osteoarthritis			
subjects affected / exposed	1 / 1099 (0.09%)	9 / 1517 (0.59%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 10	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Patellofemoral pain syndrome			
subjects affected / exposed	0 / 1099 (0.00%)	0 / 1517 (0.00%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotator cuff syndrome			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Synovial cyst			

subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spondylolisthesis			
subjects affected / exposed	0 / 1099 (0.00%)	4 / 1517 (0.26%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal stenosis			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal deformity			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Infections and infestations			
Abscess soft tissue			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Acute sinusitis			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Burn infection			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	3 / 1099 (0.27%)	3 / 1517 (0.20%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	1 / 3	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis perforated			

subjects affected / exposed	0 / 1099 (0.00%)	2 / 1517 (0.13%)	0 / 546 (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
Bacteraemia			
subjects affected / exposed	1 / 1099 (0.09%)	2 / 1517 (0.13%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial infection			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Bronchitis			
subjects affected / exposed	0 / 1099 (0.00%)	3 / 1517 (0.20%)	0 / 546 (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
Appendiceal abscess			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Campylobacter gastroenteritis			
subjects affected / exposed	0 / 1099 (0.00%)	0 / 1517 (0.00%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	2 / 1099 (0.18%)	3 / 1517 (0.20%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	1 / 2	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Central nervous system infection			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Chorioretinitis			

subjects affected / exposed	1 / 1099 (0.09%)	2 / 1517 (0.13%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic sinusitis			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Complicated appendicitis			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
COVID-19 pneumonia			
subjects affected / exposed	0 / 1099 (0.00%)	6 / 1517 (0.40%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 2	0 / 0
Diarrhoea infectious			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Diverticulitis			
subjects affected / exposed	1 / 1099 (0.09%)	3 / 1517 (0.20%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalitis viral			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Enterovirus infection			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Escherichia urinary tract infection			

subjects affected / exposed	1 / 1099 (0.09%)	2 / 1517 (0.13%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	0 / 1099 (0.00%)	14 / 1517 (0.92%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 14	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cystitis			
subjects affected / exposed	0 / 1099 (0.00%)	4 / 1517 (0.26%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 0	4 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	2 / 1099 (0.18%)	7 / 1517 (0.46%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 2	0 / 8	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis proteus			
subjects affected / exposed	0 / 1099 (0.00%)	0 / 1517 (0.00%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal infection			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Groin abscess			
subjects affected / exposed	0 / 1099 (0.00%)	2 / 1517 (0.13%)	0 / 546 (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
Hepatitis E			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Herpes zoster			

subjects affected / exposed	1 / 1099 (0.09%)	5 / 1517 (0.33%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	1 / 1	5 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ophthalmic herpes zoster			
subjects affected / exposed	0 / 1099 (0.00%)	2 / 1517 (0.13%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	1 / 1099 (0.09%)	6 / 1517 (0.40%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 6	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Labyrinthitis			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Lower respiratory tract infection			
subjects affected / exposed	0 / 1099 (0.00%)	4 / 1517 (0.26%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis cryptococcal			
subjects affected / exposed	0 / 1099 (0.00%)	2 / 1517 (0.13%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal abscess			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Herpes zoster meningitis			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Oral viral infection			

subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Orchitis			
subjects affected / exposed	0 / 1099 (0.00%)	2 / 1517 (0.13%)	0 / 546 (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
Otosalpingitis			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Parainfluenzae virus infection			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Peritonitis			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 1099 (0.09%)	28 / 1517 (1.85%)	2 / 546 (0.37%)
occurrences causally related to treatment / all	0 / 1	6 / 31	1 / 2
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Pulmonary tuberculosis			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Pneumonia bacterial			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pneumonia influenzal			

subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Pneumonia legionella			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Postoperative wound infection			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Progressive multifocal leukoencephalopathy			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Pneumonia aspiration			
subjects affected / exposed	1 / 1099 (0.09%)	4 / 1517 (0.26%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 4	0 / 0
deaths causally related to treatment / all	1 / 1	1 / 2	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 1099 (0.00%)	9 / 1517 (0.59%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 0	3 / 9	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis chronic			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Respiratory tract infection			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Rhinovirus infection			

subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Sepsis			
subjects affected / exposed	1 / 1099 (0.09%)	15 / 1517 (0.99%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 1	4 / 15	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Septic encephalopathy			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Urosepsis			
subjects affected / exposed	5 / 1099 (0.45%)	13 / 1517 (0.86%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	1 / 5	3 / 15	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 3	0 / 0
Subcutaneous abscess			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Tooth abscess			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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	3 / 1099 (0.27%)	4 / 1517 (0.26%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 3	1 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	15 / 1099 (1.36%)	67 / 1517 (4.42%)	7 / 546 (1.28%)
occurrences causally related to treatment / all	9 / 32	25 / 109	3 / 8
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Urinary tract infection bacterial			

subjects affected / exposed	0 / 1099 (0.00%)	3 / 1517 (0.20%)	0 / 546 (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
Septic shock			
subjects affected / exposed	2 / 1099 (0.18%)	7 / 1517 (0.46%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 7	0 / 0
deaths causally related to treatment / all	1 / 1	1 / 3	0 / 0
Vestibular neuronitis			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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 / 1099 (0.00%)	2 / 1517 (0.13%)	0 / 546 (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
Wound infection			
subjects affected / exposed	0 / 1099 (0.00%)	0 / 1517 (0.00%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Metabolism and nutrition disorders			
Shock hypoglycaemic			
subjects affected / exposed	0 / 1099 (0.00%)	0 / 1517 (0.00%)	1 / 546 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lactic acidosis			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Iron deficiency			

subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Hypokalaemia			
subjects affected / exposed	0 / 1099 (0.00%)	2 / 1517 (0.13%)	0 / 546 (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
Hyperkalaemia			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Hyperglycaemic crisis			
subjects affected / exposed	0 / 1099 (0.00%)	1 / 1517 (0.07%)	0 / 546 (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
Haemochromatosis			
subjects affected / exposed	1 / 1099 (0.09%)	1 / 1517 (0.07%)	0 / 546 (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
Dehydration			
subjects affected / exposed	2 / 1099 (0.18%)	4 / 1517 (0.26%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 1099 (0.00%)	2 / 1517 (0.13%)	0 / 546 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Core-BAF312	All BAF312	Core-Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	778 / 1099 (70.79%)	1267 / 1517 (83.52%)	348 / 546 (63.74%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	45 / 1099 (4.09%)	130 / 1517 (8.57%)	15 / 546 (2.75%)
occurrences (all)	53	167	17
Vascular disorders			
Hypertension			
subjects affected / exposed	114 / 1099 (10.37%)	294 / 1517 (19.38%)	41 / 546 (7.51%)
occurrences (all)	126	328	41
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	100 / 1099 (9.10%)	171 / 1517 (11.27%)	51 / 546 (9.34%)
occurrences (all)	112	191	54
Oedema peripheral			
subjects affected / exposed	50 / 1099 (4.55%)	107 / 1517 (7.05%)	13 / 546 (2.38%)
occurrences (all)	53	123	14
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	35 / 1099 (3.18%)	90 / 1517 (5.93%)	18 / 546 (3.30%)
occurrences (all)	40	102	23
Psychiatric disorders			
Depression			
subjects affected / exposed	43 / 1099 (3.91%)	134 / 1517 (8.83%)	28 / 546 (5.13%)
occurrences (all)	44	143	31
Insomnia			
subjects affected / exposed	37 / 1099 (3.37%)	84 / 1517 (5.54%)	19 / 546 (3.48%)
occurrences (all)	39	89	20
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	58 / 1099 (5.28%)	108 / 1517 (7.12%)	8 / 546 (1.47%)
occurrences (all)	70	141	10
Gamma-glutamyltransferase increased			

subjects affected / exposed	43 / 1099 (3.91%)	120 / 1517 (7.91%)	6 / 546 (1.10%)
occurrences (all)	51	156	6
Lymphocyte count decreased			
subjects affected / exposed	4 / 1099 (0.36%)	84 / 1517 (5.54%)	0 / 546 (0.00%)
occurrences (all)	6	112	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	126 / 1099 (11.46%)	295 / 1517 (19.45%)	59 / 546 (10.81%)
occurrences (all)	205	670	93
Contusion			
subjects affected / exposed	34 / 1099 (3.09%)	96 / 1517 (6.33%)	15 / 546 (2.75%)
occurrences (all)	41	127	15
Nervous system disorders			
Muscle spasticity			
subjects affected / exposed	41 / 1099 (3.73%)	89 / 1517 (5.87%)	23 / 546 (4.21%)
occurrences (all)	47	107	23
Headache			
subjects affected / exposed	158 / 1099 (14.38%)	249 / 1517 (16.41%)	71 / 546 (13.00%)
occurrences (all)	244	388	93
Dizziness			
subjects affected / exposed	74 / 1099 (6.73%)	145 / 1517 (9.56%)	26 / 546 (4.76%)
occurrences (all)	89	184	31
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	9 / 1099 (0.82%)	137 / 1517 (9.03%)	0 / 546 (0.00%)
occurrences (all)	9	173	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	39 / 1099 (3.55%)	103 / 1517 (6.79%)	21 / 546 (3.85%)
occurrences (all)	43	119	29
Diarrhoea			
subjects affected / exposed	69 / 1099 (6.28%)	119 / 1517 (7.84%)	22 / 546 (4.03%)
occurrences (all)	82	169	24
Nausea			
subjects affected / exposed	73 / 1099 (6.64%)	119 / 1517 (7.84%)	19 / 546 (3.48%)
occurrences (all)	84	143	22

Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	15 / 1099 (1.36%)	80 / 1517 (5.27%)	6 / 546 (1.10%)
occurrences (all)	16	113	8
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	60 / 1099 (5.46%)	113 / 1517 (7.45%)	21 / 546 (3.85%)
occurrences (all)	75	154	28
Back pain			
subjects affected / exposed	65 / 1099 (5.91%)	186 / 1517 (12.26%)	43 / 546 (7.88%)
occurrences (all)	77	228	47
Arthralgia			
subjects affected / exposed	69 / 1099 (6.28%)	184 / 1517 (12.13%)	42 / 546 (7.69%)
occurrences (all)	83	248	54
Infections and infestations			
Bronchitis			
subjects affected / exposed	36 / 1099 (3.28%)	94 / 1517 (6.20%)	16 / 546 (2.93%)
occurrences (all)	42	115	18
COVID-19			
subjects affected / exposed	0 / 1099 (0.00%)	189 / 1517 (12.46%)	0 / 546 (0.00%)
occurrences (all)	0	206	0
Urinary tract infection			
subjects affected / exposed	128 / 1099 (11.65%)	369 / 1517 (24.32%)	75 / 546 (13.74%)
occurrences (all)	209	900	130
Upper respiratory tract infection			
subjects affected / exposed	89 / 1099 (8.10%)	165 / 1517 (10.88%)	41 / 546 (7.51%)
occurrences (all)	107	244	55
Nasopharyngitis			
subjects affected / exposed	149 / 1099 (13.56%)	325 / 1517 (21.42%)	79 / 546 (14.47%)
occurrences (all)	215	620	128
Influenza			
subjects affected / exposed	72 / 1099 (6.55%)	152 / 1517 (10.02%)	40 / 546 (7.33%)
occurrences (all)	87	194	46
Herpes zoster			

subjects affected / exposed	24 / 1099 (2.18%)	92 / 1517 (6.06%)	4 / 546 (0.73%)
occurrences (all)	25	97	4
Cystitis			
subjects affected / exposed	28 / 1099 (2.55%)	79 / 1517 (5.21%)	13 / 546 (2.38%)
occurrences (all)	43	135	18
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	28 / 1099 (2.55%)	99 / 1517 (6.53%)	11 / 546 (2.01%)
occurrences (all)	31	102	12

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 May 2014	• Based on the available treatment initiation cardiac monitoring results, the 6 hour post-dose first dose observation (Day 1 and 7) in subjects with normal cardiovascular status could be discontinued. Continued data capture with mobile cardiac telemetry (MCT) and Holter in all patients was supported, to facilitate the assessment of any relevant events occurring during treatment initiation. • To harmonize the Treatment Epoch between the protocol and eCRF. • To allow the use of beta-blockers. • To modify inclusion/exclusion criteria on use of contraception, and to provide exclusion criteria for 2 additional medications that had been approved for the treatment of MS (dimethyl fumarate and teriflunomide) after the original protocol was written. • To update details on potent CYP2C9 inhibitors. • To require any patient who missed any dose during the titration phase to restart dose titration.
05 March 2015	• To update the rule and the timing for the planned futility analysis. • To add clarity and specific considerations for concomitant treatment, regarding potential interruption of beta-blocker treatment in patients with resting heart rate ≤50 bpm before introducing siponimod/placebo treatment. • Details on "emergency breaking of treatment assignment" were updated. • Completion of the blinded data review for sample size re-estimation was mentioned, specifically confirming that the number of patients to be enrolled would not increase.
06 October 2015	• An Extension Part was incorporated into the study design. • Designations of Core Part and Extension Part were added in the descriptions of protocol elements, as applicable. • The stopping criterion for the Core Part of the study was updated. Specifically, the Core Part of the study was to be stopped approximately 3 years after the randomization of the first patient.
23 March 2016	• To specify and justify the overall study duration in the protocol to accommodate the different regulations applicable in various countries. • To make the Month 1 extension visit optional for patients who had been on open-label siponimod in the Core Part for at least 6 continuous months immediately before starting the Extension Part of the study, to avoid repeat procedures for these patients • To clarify that the Day 4 extension visit was only for patients who required first-dose monitoring and for whom this was conducted with a Holter monitor. Collection of vital signs became optional. • To clarify that the Day 7 extension visit was not needed for patients who were entering the Extension Part from open-label siponimod treatment without a break of 4 days of treatment, as no first dose monitoring was needed for these patients. • Reference to the Extension Part continuing "for at least 1 year after approval in major markets for the treatment of SPMS" was removed to provide consistency with the 84 month Schedule of Assessments. • Month 84 visit was removed from the Schedule of Assessments and designated as the end of study (EOS) visit. • Changes to the SAE language section and an addition to the ethical considerations section of the protocol were made to comply with the latest guidelines a new protocol template. • The Early Study Termination section was updated to include reasons of risk/benefit, regulatory or medical reasons to comply with current template language. • The reference to electronic EDSS was removed to allow the Sponsor to switch to other EDSS methodologies. • Changes were made to statistical sections to include baseline as a covariate for the T25W analysis (to be consistent with other analyses).

28 July 2020	● To change cardiac assessments and monitoring requirements during dose titration for dose re-start. ● To add an additional pulmonary function test (PFT) assessment to the follow-up (FU) visit to provide additional PFT data after patients discontinued treatment with siponimod. ● To introduce the consideration of reduction in maintenance dose from 2.0 mg/ day to 1.0 mg/ day for patients with *1/*3 or *2/*3 CYP2C9 genotype. ● To introduce the possibility to collect safety information remotely and ship investigational medicinal product (IMP) directly to patients' home, in situation it is not safe for them to attend on-site visit, in response to the COVID-19 pandemics (or similar pandemics).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported