Clinical trial results:
A Multinational, Multicenter, Open-Label, Single-Assignment Extension of the MS-LAQ-302 (BRAVO) Study to Evaluate the Long-Term Safety, Tolerability, and Effect on Disease Course of Daily Oral Laquinimod 0.6 mg in Subjects with Relapsing Multiple Sclerosis

Summary

EudraCT number	2009-015815-42
Trial protocol	EE IT ES CZ SK PL BG LT DE
Global end of trial date	30 June 2017

Results information

Result version number	v1 (current)
This version publication date	24 January 2019
First version publication date	24 January 2019

Trial information

Trial identification

Sponsor protocol code	MS-LAQ-302E

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01047319
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Teva Pharmaceutical Industries, Ltd
Sponsor organisation address	5 Basel Street, Petach-Tikva, Israel, 49131
Public contact	Director, Clinical Research, Teva Pharmaceutical Industries, Ltd, 001 888-483-8279, info.era-clinical@teva.de
Scientific contact	Director, Clinical Research, Teva Pharmaceutical Industries, Ltd, 001 888-483-8279, info.era-clinical@teva.de

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 March 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 June 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The objectives of the study were as follows:
- To make treatment with oral laquinimod 0.6 mg available to all subjects who participated in the MS-LAQ-302 study (regardless of their treatment assignment, whether oral or injectable) and who completed the termination visit of this study according to the MS-LAQ-302 protocol as long as the Sponsor continued the development of laquinimod 0.6 mg for relapsing-remitting multiple sclerosis (RRMS).
- To assess the long-term safety and tolerability of laquinimod 0.6 mg once daily in patients with RRMS.
- To assess the long-term effects of laquinimod 0.6 mg on the disease course, as measured by clinical efficacy outcomes, which were evaluated in the MS-LAQ-302 study in this subject population.

Protection of trial subjects:

Written and/or oral information about the study was provided to all patients in a language understandable by the patients. The information included an adequate explanation of the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force. Written informed consent was obtained from each patient before any study procedures or assessments were done. It was explained to the patients that they were free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.
Each patient’s willingness to participate in the study was documented in writing in a consent form that was signed by the patient with the date of that signature indicated. Each Investigator kept the original consent forms, and copies were given to the patients.
This study includes the following separate informed consent forms:
- an informed consent form at the baseline visit
- an informed consent for patients who were permitted by the Sponsor to re-enroll in the study following study discontinuation due to a planned pregnancy (introduced by Global Protocol Amendment 1)

As of 25 February 2016, a separate reconsent form that described the cardiovascular risk findings at higher doses of laquinimod (1.2 and 1.5 mg/day) was required to be signed by all patients, as introduced by Global Protocol Amendment 2 .

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 May 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 134
Country: Number of subjects enrolled	Czech Republic: 28
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	Spain: 14

Country: Number of subjects enrolled	Estonia: 14
Country: Number of subjects enrolled	Georgia: 36
Country: Number of subjects enrolled	Croatia: 39
Country: Number of subjects enrolled	Israel: 16
Country: Number of subjects enrolled	Italy: 30
Country: Number of subjects enrolled	Lithuania: 20
Country: Number of subjects enrolled	Macedonia, the former Yugoslav Republic of: 18
Country: Number of subjects enrolled	Poland: 187
Country: Number of subjects enrolled	Romania: 67
Country: Number of subjects enrolled	Russian Federation: 99
Country: Number of subjects enrolled	Slovakia: 17
Country: Number of subjects enrolled	Ukraine: 234
Country: Number of subjects enrolled	United States: 61
Country: Number of subjects enrolled	South Africa: 26
Worldwide total number of subjects	1047
EEA total number of subjects	557

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)	1047
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

All participants who completed the full duration of the double-blind BRAVO study (study MS-LAQ-302) were eligible to enter into Study MS-LAQ-302E. Of the 1090 participants who completed MS-LAQ-302, 1047 opted to continue into the open-label extension study.

Pre-assignment

Screening details:

1047 subjects with RRMS were enrolled to receive laquinimod 0.6 mg daily at 144 study sites in 18 countries by 144 investigators.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Early laquinimod

Arm description:

All participants in MS-LAQ-302E were administered 1 capsule containing laquinimod 0.6 mg taken orally at the same hour every day until the product was commercially available or development stopped. The Early laquinimod subgroup included participants in MS-LAQ-302 double-blind study who were administered laquinimod 0.6 mg daily for 24 months.

Arm type	Experimental
Investigational medicinal product name	laquinimod
Investigational medicinal product code	
Other name	TV-5600
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

One capsule of laquinimod 0.6 mg was taken orally at the same hour every day.

Arm title	Switch from placebo

Arm description:

All participants in MS-LAQ-302E were administered 1 capsule containing laquinimod 0.6 mg taken orally at the same hour every day until the product was commercially available or development stopped. The Switch from placebo subgroup included participants in MS-LAQ-302 double-blind study who were administered placebo daily for 24 months.

Arm type	Experimental
Investigational medicinal product name	laquinimod
Investigational medicinal product code	
Other name	TV-5600
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

One capsule of laquinimod 0.6 mg was taken orally at the same hour every day.

Arm title	Switch from Avonex

Arm description:

All participants in MS-LAQ-302E were administered 1 capsule containing laquinimod 0.6 mg taken orally at the same hour every day until the product was commercially available or development stopped. The Switch from Avonex subgroup included participants in MS-LAQ-302 rater-blind study who were administered Avonex 30 mcg IM once weekly for 24 months.

Arm type	Experimental
Investigational medicinal product name	laquinimod
Investigational medicinal product code	
Other name	TV-5600
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

One capsule of laquinimod 0.6 mg was taken orally at the same hour every day.

Number of subjects in period 1	Early laquinimod	Switch from placebo	Switch from Avonex
Started	345	350	352
Completed	0	0	0
Not completed	345	350	352
Adverse event, serious fatal	5	1	5
Physician decision	12	9	10
Consent withdrawn by subject	77	75	87
Study terminated by Sponsor	198	215	203
Adverse event, non-fatal	16	27	21
Teva requested participant withdrawal	3	-	1
Pregnancy	13	8	8
Lost to follow-up	14	10	10
Protocol deviation	3	2	4
Lack of efficacy	4	3	3

Baseline characteristics

Reporting groups	
Reporting group title	Early laquinimod
Reporting group description:	
All participants in MS-LAQ-302E were administered 1 capsule containing laquinimod 0.6 mg taken orally at the same hour every day until the product was commercially available or development stopped. The Early laquinimod subgroup included participants in MS-LAQ-302 double-blind study who were administered laquinimod 0.6 mg daily for 24 months.	
Reporting group title	Switch from placebo
Reporting group description:	
All participants in MS-LAQ-302E were administered 1 capsule containing laquinimod 0.6 mg taken orally at the same hour every day until the product was commercially available or development stopped. The Switch from placebo subgroup included participants in MS-LAQ-302 double-blind study who were administered placebo daily for 24 months.	
Reporting group title	Switch from Avonex
Reporting group description:	
All participants in MS-LAQ-302E were administered 1 capsule containing laquinimod 0.6 mg taken orally at the same hour every day until the product was commercially available or development stopped. The Switch from Avonex subgroup included participants in MS-LAQ-302 rater-blind study who were administered Avonex 30 mcg IM once weekly for 24 months.	

Reporting group values	Early laquinimod	Switch from placebo

Reporting group values	Total		
Number of subjects	1047		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	1047		
From 65-84 years	0		
85 years and over	0		
Age Continuous Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Subjects			
Female	707		
Male	340		
Race/Ethnicity, Customized Units: Subjects			
Asian/Oriental	2		
Black/African American	6		
White	1032		
Unknown	4		
Other	3		

End points

End points reporting groups

Reporting group title	Early laquinimod

Reporting group description:

All participants in MS-LAQ-302E were administered 1 capsule containing laquinimod 0.6 mg taken orally at the same hour every day until the product was commercially available or development stopped. The Early laquinimod subgroup included participants in MS-LAQ-302 double-blind study who were administered laquinimod 0.6 mg daily for 24 months.

Reporting group title	Switch from placebo

Reporting group description:

All participants in MS-LAQ-302E were administered 1 capsule containing laquinimod 0.6 mg taken orally at the same hour every day until the product was commercially available or development stopped. The Switch from placebo subgroup included participants in MS-LAQ-302 double-blind study who were administered placebo daily for 24 months.

Reporting group title	Switch from Avonex

Reporting group description:

All participants in MS-LAQ-302E were administered 1 capsule containing laquinimod 0.6 mg taken orally at the same hour every day until the product was commercially available or development stopped. The Switch from Avonex subgroup included participants in MS-LAQ-302 rater-blind study who were administered Avonex 30 mcg IM once weekly for 24 months.

Primary: Participants with Treatment-Emergent Adverse Events (TEAEs)

End point title	Participants with Treatment-Emergent Adverse Events

End point description:

A treatment-emergent adverse event was defined as any untoward medical occurrence that develops or worsens in severity following start of treatment and does not necessarily have a causal relationship to the study drug. Severity was rated by the investigator on a scale of mild, moderate and severe, with severe= an AE which prevents normal daily activities. Relation of AE to treatment was determined by the investigator. Serious AEs (SAE) include death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, a congenital anomaly or birth defect, OR an important medical event that jeopardized the patient and required medical intervention to prevent the previously listed serious outcomes. TEAEs associated with cancer, ischemic heart disease, cerebrovascular events, and arthritis were considered to be of special interest.

End point type	Primary

End point timeframe:

Day 1 up to 7.13 years

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No intention to make inference based on stat analysis; the intent is to support clinical judgment.

End point values	Early laquinimod	Switch from placebo	Switch from Avonex	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	345	350	352	
Units: participants				
=>1 TEAE|	290	303	279	
=>1 Serious TEAE|	54	65	51	
=>1 Severe TEAE|	36	54	44	
=>1 TEAE causing discontinuation|	20	28	23	
=>1 TEAE of special interest|	66	64	73	

=>1 treatment-related TEAE|	66	76	96	
=>1 TEAE leading to death|	5	3	5	

Statistical analyses

No statistical analyses for this end point

Secondary: Participants with Potentially Clinically Significant Abnormal Vital Signs

End point title	Participants with Potentially Clinically Significant Abnormal Vital Signs

End point description:

Vital signs with potentially clinically significant abnormal results were evaluated using the following significance criteria: - Pulse rate: >=120 and increase >=30 beats/minute - Systolic blood pressure low: <=90 and decrease >=30 mmHg - Systolic blood pressure high: >=180 and increase >=30 mmHg - Diastolic blood pressure low: <=50 and decrease >=20 mmHg - Diastolic blood pressure high: >=100 and increase >=20 mmHg Note that the change is compared to baseline,

End point type	Secondary

End point timeframe:

Baseline (Day 0 for extension), Day 1 up to 7.13 years

End point values	Early laquinimod	Switch from placebo	Switch from Avonex	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	345	350	352	
Units: participants				
Participants with at least one abnormality|	19	23	19	
Pulse rate - high|	2	0	0	
Systolic blood pressure - low|	4	7	9	
Systolic blood pressure - high|	0	2	0	
Diastolic blood pressure - low|	4	5	4	
Diastolic blood pressure - high|	9	10	7	

Statistical analyses

No statistical analyses for this end point

Secondary: Participants with Serum Chemistry Laboratory Tests That Were Potentially Clinically Significant (PCS) Abnormal Comparing Baseline to Any Time During the Study

End point title	Participants with Serum Chemistry Laboratory Tests That Were Potentially Clinically Significant (PCS) Abnormal Comparing Baseline to Any Time During the Study

End point description:

Counts include two conditions: - a change from High / Non-PCS at baseline to Low PCS at any point during the study - a change from Low / Non-PCS at baseline to High PCS at any point during the study

Participants whose condition was not changed from baseline or was changed to a non-PCS value are included in the population count. ALT=alanine aminotransferase ALP=alkaline phosphatase P-amylase=amylase, pancreatic AST=aspartate aminotransferase CRP=C reactive protein CK=creatine kinase CTN=creatinine FIB=fibrinogen GGT=gamma glutamyl transferase K=potassium

End point type	Secondary

End point timeframe:

Baseline (Day 0), Day 1 to 7.13 years

End point values	Early laquinimod	Switch from placebo	Switch from Avonex	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	344	349	347	
Units: participants				
ALT - change from Low / Non-PCS to High PCS|	5	8	10	
Albumen - change from High / Non-PCS to Low PCS|	0	1	0	
ALP - change from Low / Non-PCS to High PCS|	0	2	0	
p-Amylase - change from Low / Non-PCS to High PCS|	5	1	2	
AST - change from Low / Non-PCS to High PCS|	3	2	5	
Bilirubin - change from Low / Non-PCS to High PCS|	2	3	2	
CRP - change from Low / Non-PCS to High PCS|	36	32	31	
Calcium - change from High / Non-PCS to Low PCS|	1	1	1	
Calcium - change from Low / Non-PCS to High PCS|	1	1	2	
CK - change from Low / Non-PCS to High PCS|	11	12	10	
CTN - change from Low / Non-PCS to High PCS|	1	1	0	
FIB - change from Low / Non-PCS to High PCS|	22	24	25	
GGT - change from Low / Non-PCS to High PCS|	16	22	18	
Glucose - change from High / Non-PCS to Low PCS|	12	16	11	
Glucose - change from Low / Non-PCS to High PCS|	4	5	2	
Phosphate-change from High / Non-PCS to Low PCS|	12	12	6	
Phosphate-change from Low / Non-PCS to High PCS|	17	18	16	
K - change from High / Non-PCS to Low PCS|	2	4	2	
K - change from Low / Non-PCS to High PCS|	46	39	38	
Sodium - change from High / Non-PCS to Low PCS|	4	2	3	
Sodium - change from Low / Non-PCS to High PCS|	21	16	17	
Urea - change from Low / Non-PCS to High PCS|	4	4	3	

Statistical analyses

No statistical analyses for this end point

Secondary: Participants with Serum Hematology Laboratory Tests That Were Potentially Clinically Significant (PCS) Abnormal Comparing Baseline to Any Time During the Study

End point title	Participants with Serum Hematology Laboratory Tests That Were Potentially Clinically Significant (PCS) Abnormal Comparing Baseline to Any Time During the Study

End point description:

Counts include two conditions: - a change from High / Non-PCS at baseline to Low PCS at any point during the study - a change from Low / Non-PCS at baseline to High PCS at any point during the study Participants whose condition was not changed from baseline or was changed to a non-PCS value are included in the population count.

End point type	Secondary

End point timeframe:

Baseline (Day 0), Day 1 to 7.13 years

End point values	Early laquinimod	Switch from placebo	Switch from Avonex	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	344	349	347	
Units: participants				
Hematocrit-change from High/Non-PCS to Low PCS	30	25	21	
Hemoglobin-change from High/Non-PCS to Low PCS	21	24	15	
Leukocytes-change from High/Non-PCS to Low PCS	2	4	2	
Leukocytes-change from Low/Non-PCS to High PCS	4	1	5	
Neutrophils-change from High/Non-PCS to Low PCS	25	12	14	
Platelets-change from High/Non-PCS to Low PCS	5	3	2	
Platelets-change from Low/Non-PCS to High PCS	4	4	4	

Statistical analyses

No statistical analyses for this end point

Secondary: Participants with Electrocardiogram (ECG) Fiindings That Shifted from

Baseline to Any Time During the Study

End point title	Participants with Electrocardiogram (ECG) Fiindings That Shifted from Baseline to Any Time During the Study

End point description:

Shifts are presented as Baseline finding / Worse finding at anytime during the study. Categories for findings are: - normal - abnormal, not clinically significant (Not CS) - abnormal, clinically significant (CS)

End point type	Secondary

End point timeframe:

Baseline (Day 0), Day 1 to 7.13 years

End point values	Early laquinimod	Switch from placebo	Switch from Avonex	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	340	346	345	
Units: participants				
Normal / Normal	150	148	134	
Normal / Abnormal, Not CS	109	125	119	
Normal / Abnormal, CS	5	3	5	
Abnormal, Not CS / Normal	5	7	20	
Abnormal, Not CS / Abnormal, Not CS	67	62	64	
Abnormal, Not CS / Abnormal, CS	4	0	2	
Abnormal, CS / Normal	0	0	0	
Abnormal, CS / Abnormal, Not CS	0	0	1	
Abnormal, CS / Abnormal, CS	0	1	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Day 1 up to 7.13 years	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0
Reporting groups	
Reporting group title	Early laquinimod
Reporting group description: All participants in MS-LAQ- 302E were administered 1 capsule containing laquinimod 0.6 mg taken orally at the same hour every day until the product was commercially available or development stopped. The Early laquinimod subgroup included participants in MS-LAQ-302 double-blind study who were administered laquinimod 0.6 mg daily for 24 months.	
Reporting group title	Switch from Avonex
Reporting group description: All participants in MS-LAQ- 302E were administered 1 capsule containing laquinimod 0.6 mg taken orally at the same hour every day until the product was commercially available or development stopped. The Switch from Avonex subgroup included participants in MS-LAQ-302 rater-blind study who were administered Avonex 30 mcg IM once weekly for 24 months.	
Reporting group title	Switch from Placebo
Reporting group description: All participants in MS-LAQ- 302E were administered 1 capsule containing laquinimod 0.6 mg taken orally at the same hour every day until the product was commercially available or development stopped. The Switch from Placebo subgroup included participants in MS-LAQ-302 double-blind study who were administered placebo daily for 24 months.	

Serious adverse events	Early laquinimod	Switch from Avonex	Switch from Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	54 / 345 (15.65%)	51 / 352 (14.49%)	65 / 350 (18.57%)
number of deaths (all causes)	5	5	3
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute leukaemia			
subjects affected / exposed	1 / 345 (0.29%)	0 / 352 (0.00%)	0 / 350 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Adenocarcinoma			
subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Adenocarcinoma of colon			
subjects affected / exposed	1 / 345 (0.29%)	0 / 352 (0.00%)	0 / 350 (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
Basal cell carcinoma			
subjects affected / exposed	1 / 345 (0.29%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
subjects affected / exposed	1 / 345 (0.29%)	0 / 352 (0.00%)	0 / 350 (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
Breast cancer stage II			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	0 / 350 (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
Cervix carcinoma stage II			
subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fibrous histiocytoma			
subjects affected / exposed	1 / 345 (0.29%)	0 / 352 (0.00%)	0 / 350 (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
Intraductal proliferative breast lesion			
subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 345 (0.29%)	1 / 352 (0.28%)	0 / 350 (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
Keratoacanthoma			

subjects affected / exposed	1 / 345 (0.29%)	0 / 352 (0.00%)	0 / 350 (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
Malignant melanoma			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	0 / 350 (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
Malignant melanoma in situ			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	0 / 350 (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
Malignant neoplasm of renal pelvis			
subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to liver			
subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	2 / 350 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Neuroma			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	0 / 350 (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-small cell lung cancer metastatic			
subjects affected / exposed	1 / 345 (0.29%)	0 / 352 (0.00%)	0 / 350 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Papillary thyroid cancer			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	0 / 350 (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 adenocarcinoma			

subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	0 / 350 (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 cancer			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Squamous cell carcinoma of the cervix			
subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine cancer			
subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	2 / 350 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	3 / 345 (0.87%)	3 / 352 (0.85%)	4 / 350 (1.14%)
occurrences causally related to treatment / all	0 / 4	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic rupture			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	0 / 350 (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
Circulatory collapse			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	0 / 350 (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
Deep vein thrombosis			
subjects affected / exposed	0 / 345 (0.00%)	2 / 352 (0.57%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolaemic shock			

subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	0 / 350 (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
Internal haemorrhage			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	0 / 350 (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
Jugular vein thrombosis			
subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombophlebitis superficial			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	0 / 350 (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
Surgical and medical procedures			
Bartholin's cyst removal			
subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystectomy			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	0 / 350 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture reduction			
subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hysterectomy			
subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia repair			

Pyrexia			
subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Allergy to metals			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	0 / 350 (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
Food allergy			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	0 / 350 (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
Reproductive system and breast disorders			
Bartholin's cyst			
subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical dysplasia			
subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	3 / 350 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical polyp			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	0 / 350 (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 disorder			
subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometriosis			
subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	4 / 350 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Menorrhagia			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Menstrual disorder			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	0 / 350 (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
Metrorrhagia			
subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cyst ruptured			
subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	2 / 350 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian haemorrhage			
subjects affected / exposed	1 / 345 (0.29%)	0 / 352 (0.00%)	0 / 350 (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
Pelvic adhesions			
subjects affected / exposed	1 / 345 (0.29%)	0 / 352 (0.00%)	0 / 350 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postmenopausal haemorrhage			
subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine polyp			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	0 / 350 (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
Vaginal cyst			

subjects affected / exposed	1 / 345 (0.29%)	0 / 352 (0.00%)	0 / 350 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Chronic respiratory failure			
subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paranasal cyst			
subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	1 / 345 (0.29%)	1 / 352 (0.28%)	0 / 350 (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
Pleurisy			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	0 / 350 (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
Pulmonary oedema			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	0 / 350 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Alcohol withdrawal syndrome			
subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Completed suicide			
subjects affected / exposed	1 / 345 (0.29%)	0 / 352 (0.00%)	0 / 350 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	0 / 350 (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 / 345 (0.00%)	1 / 352 (0.28%)	0 / 350 (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
Mood disorder due to a general medical condition			
subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Panic attack			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	0 / 350 (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
Product issues			
Device loosening			
subjects affected / exposed	1 / 345 (0.29%)	0 / 352 (0.00%)	0 / 350 (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
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	0 / 350 (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
Cholecystitis			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cholecystitis chronic			
subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	1 / 345 (0.29%)	1 / 352 (0.28%)	0 / 350 (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
Hepatitis toxic			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	0 / 350 (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
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	1 / 345 (0.29%)	0 / 352 (0.00%)	0 / 350 (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
Injury, poisoning and procedural complications			
Accident			
subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Animal bite			
subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle fracture			
subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical vertebral fracture			
subjects affected / exposed	1 / 345 (0.29%)	0 / 352 (0.00%)	0 / 350 (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

Concussion			
subjects affected / exposed	1 / 345 (0.29%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Contusion			
subjects affected / exposed	1 / 345 (0.29%)	0 / 352 (0.00%)	0 / 350 (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
Craniocerebral injury			
subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epiphyseal fracture			
subjects affected / exposed	1 / 345 (0.29%)	0 / 352 (0.00%)	0 / 350 (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
Facial bones fracture			
subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	1 / 345 (0.29%)	1 / 352 (0.28%)	0 / 350 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	1 / 345 (0.29%)	1 / 352 (0.28%)	0 / 350 (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
Joint dislocation			

subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	2 / 350 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament sprain			
subjects affected / exposed	1 / 345 (0.29%)	0 / 352 (0.00%)	0 / 350 (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
Meniscus injury			
subjects affected / exposed	1 / 345 (0.29%)	0 / 352 (0.00%)	0 / 350 (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
Pneumothorax traumatic			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	0 / 350 (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
Radius fracture			
subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	2 / 350 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	1 / 345 (0.29%)	1 / 352 (0.28%)	0 / 350 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Skeletal injury			
subjects affected / exposed	1 / 345 (0.29%)	0 / 352 (0.00%)	0 / 350 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Splenic rupture			
subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	1 / 350 (0.29%)
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	0 / 345 (0.00%)	1 / 352 (0.28%)	0 / 350 (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	1 / 345 (0.29%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulna fracture			
subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			
subjects affected / exposed	1 / 345 (0.29%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureteric injury			
subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound			
subjects affected / exposed	1 / 345 (0.29%)	0 / 352 (0.00%)	0 / 350 (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
Congenital, familial and genetic disorders			
Hydrocele			
subjects affected / exposed	1 / 345 (0.29%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute left ventricular failure			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	0 / 350 (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

Acute myocardial infarction			
subjects affected / exposed	2 / 345 (0.58%)	2 / 352 (0.57%)	0 / 350 (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
Arrhythmia			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	0 / 350 (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
Atrial flutter			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	0 / 350 (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 failure			
subjects affected / exposed	1 / 345 (0.29%)	0 / 352 (0.00%)	0 / 350 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure acute			
subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	1 / 345 (0.29%)	0 / 352 (0.00%)	0 / 350 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiopulmonary failure			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	0 / 350 (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
Cardiovascular insufficiency			
subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Coronary artery dissection			

subjects affected / exposed	1 / 345 (0.29%)	0 / 352 (0.00%)	0 / 350 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery stenosis			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	0 / 350 (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
Left ventricular failure			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	0 / 350 (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
Myocardial infarction			
subjects affected / exposed	0 / 345 (0.00%)	3 / 352 (0.85%)	0 / 350 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 2	0 / 0
Stress cardiomyopathy			
subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular extrasystoles			
subjects affected / exposed	1 / 345 (0.29%)	0 / 352 (0.00%)	0 / 350 (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
Ventricular fibrillation			
subjects affected / exposed	1 / 345 (0.29%)	0 / 352 (0.00%)	0 / 350 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Altered state of consciousness			

subjects affected / exposed	1 / 345 (0.29%)	0 / 352 (0.00%)	0 / 350 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain oedema			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	0 / 350 (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
Cerebral haemorrhage			
subjects affected / exposed	1 / 345 (0.29%)	0 / 352 (0.00%)	0 / 350 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	0 / 350 (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	1 / 345 (0.29%)	1 / 352 (0.28%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoaesthesia			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	0 / 350 (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
Ischaemic stroke			
subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar radiculopathy			

subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	2 / 350 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple sclerosis relapse			
subjects affected / exposed	1 / 345 (0.29%)	1 / 352 (0.28%)	0 / 350 (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
Muscle spasticity			
subjects affected / exposed	1 / 345 (0.29%)	0 / 352 (0.00%)	0 / 350 (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
Radiculopathy			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	0 / 350 (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
Sciatica			
subjects affected / exposed	1 / 345 (0.29%)	0 / 352 (0.00%)	0 / 350 (0.00%)
		0 / 0	0 / 0

subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	0 / 350 (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
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	0 / 350 (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			
Blepharitis			
subjects affected / exposed	1 / 345 (0.29%)	0 / 352 (0.00%)	0 / 350 (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
Cataract nuclear			
subjects affected / exposed	1 / 345 (0.29%)	0 / 352 (0.00%)	0 / 350 (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
Iridocyclitis			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	0 / 350 (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
Ocular hypertension			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	0 / 350 (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 hernia			
subjects affected / exposed	1 / 345 (0.29%)	0 / 352 (0.00%)	0 / 350 (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
Abdominal pain			
subjects affected / exposed	1 / 345 (0.29%)	0 / 352 (0.00%)	0 / 350 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Anal fissure			
subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Faecaloma			
subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inflammatory bowel disease			
subjects affected / exposed	1 / 345 (0.29%)	0 / 352 (0.00%)	0 / 350 (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
Inguinal hernia			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	0 / 350 (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
Irritable bowel syndrome			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	0 / 350 (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
Large intestinal obstruction			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	0 / 350 (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
Large intestine perforation			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	0 / 350 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	1 / 345 (0.29%)	0 / 352 (0.00%)	0 / 350 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			

subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis chronic			
subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proctitis			
subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	0 / 350 (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
Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	1 / 345 (0.29%)	0 / 352 (0.00%)	0 / 350 (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
Crush syndrome			
subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	1 / 345 (0.29%)	1 / 352 (0.28%)	0 / 350 (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
Hypertonic bladder			
subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Micturition disorder			

subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	0 / 350 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureterolithiasis			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	0 / 350 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary incontinence			
subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Adrenal mass			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	0 / 350 (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
Goitre			
subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperthyroidism			
subjects affected / exposed	1 / 345 (0.29%)	0 / 352 (0.00%)	0 / 350 (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
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 345 (0.58%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Bursitis			
subjects affected / exposed	1 / 345 (0.29%)	0 / 352 (0.00%)	0 / 350 (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
Intervertebral disc protrusion			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaw cyst			
subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myalgia			
subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	2 / 345 (0.58%)	0 / 352 (0.00%)	2 / 350 (0.57%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	1 / 345 (0.29%)	0 / 352 (0.00%)	0 / 350 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal osteoarthritis			
subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal wall abscess			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	0 / 350 (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
Acute hepatitis C			

subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	2 / 345 (0.58%)	1 / 352 (0.28%)	0 / 350 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carbuncle			
subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	1 / 350 (0.29%)
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	1 / 345 (0.29%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chorioretinitis			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	0 / 350 (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			
subjects affected / exposed	2 / 345 (0.58%)	0 / 352 (0.00%)	0 / 350 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia sepsis			

subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	0 / 350 (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
HIV infection			
subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	1 / 345 (0.29%)	0 / 352 (0.00%)	0 / 350 (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
Incision site abscess			
subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious pleural effusion			
subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung abscess			
subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis viral			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	0 / 350 (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
Orchitis			
subjects affected / exposed	1 / 345 (0.29%)	0 / 352 (0.00%)	0 / 350 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Papilloma viral infection			

subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	2 / 345 (0.58%)	1 / 352 (0.28%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pilonidal cyst			
subjects affected / exposed	0 / 345 (0.00%)	2 / 352 (0.57%)	0 / 350 (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
Pneumonia			
subjects affected / exposed	1 / 345 (0.29%)	2 / 352 (0.57%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pulmonary tuberculosis			
subjects affected / exposed	1 / 345 (0.29%)	2 / 352 (0.57%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	1 / 345 (0.29%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salpingo-oophoritis			
subjects affected / exposed	1 / 345 (0.29%)	0 / 352 (0.00%)	0 / 350 (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
Tuberculosis			
subjects affected / exposed	0 / 345 (0.00%)	2 / 352 (0.57%)	0 / 350 (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
Urinary tract infection			

subjects affected / exposed	3 / 345 (0.87%)	2 / 352 (0.57%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 3	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral pharyngitis			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	0 / 350 (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 upper respiratory tract infection			
subjects affected / exposed	1 / 345 (0.29%)	0 / 352 (0.00%)	0 / 350 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection staphylococcal			
subjects affected / exposed	0 / 345 (0.00%)	0 / 352 (0.00%)	1 / 350 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Lactose intolerance			
subjects affected / exposed	0 / 345 (0.00%)	1 / 352 (0.28%)	0 / 350 (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

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

Non-serious adverse events	Early laquinimod	Switch from Avonex	Switch from Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	215 / 345 (62.32%)	194 / 352 (55.11%)	205 / 350 (58.57%)
Investigations			
C-reactive protein increased			
subjects affected / exposed	19 / 345 (5.51%)	14 / 352 (3.98%)	17 / 350 (4.86%)
occurrences (all)	25	16	23
Weight increased			
subjects affected / exposed	19 / 345 (5.51%)	9 / 352 (2.56%)	11 / 350 (3.14%)
occurrences (all)	23	10	11
Vascular disorders			

Hypertension			
subjects affected / exposed	18 / 345 (5.22%)	18 / 352 (5.11%)	21 / 350 (6.00%)
occurrences (all)	22	18	23
Nervous system disorders			
Headache			
subjects affected / exposed	44 / 345 (12.75%)	74 / 352 (21.02%)	60 / 350 (17.14%)
occurrences (all)	84	128	121
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	22 / 345 (6.38%)	15 / 352 (4.26%)	20 / 350 (5.71%)
occurrences (all)	34	18	24
Psychiatric disorders			
Depression			
subjects affected / exposed	26 / 345 (7.54%)	17 / 352 (4.83%)	20 / 350 (5.71%)
occurrences (all)	26	21	21
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	21 / 345 (6.09%)	28 / 352 (7.95%)	23 / 350 (6.57%)
occurrences (all)	27	38	27
Back pain			
subjects affected / exposed	49 / 345 (14.20%)	50 / 352 (14.20%)	49 / 350 (14.00%)
occurrences (all)	74	73	72
Infections and infestations			
Bronchitis			
subjects affected / exposed	24 / 345 (6.96%)	16 / 352 (4.55%)	23 / 350 (6.57%)
occurrences (all)	26	27	29
Influenza			
subjects affected / exposed	27 / 345 (7.83%)	22 / 352 (6.25%)	25 / 350 (7.14%)
occurrences (all)	34	32	38
Nasopharyngitis			
subjects affected / exposed	52 / 345 (15.07%)	37 / 352 (10.51%)	46 / 350 (13.14%)
occurrences (all)	96	58	77
Pharyngitis			
subjects affected / exposed	11 / 345 (3.19%)	11 / 352 (3.13%)	18 / 350 (5.14%)
occurrences (all)	18	15	24
Respiratory tract infection viral			

subjects affected / exposed	20 / 345 (5.80%)	16 / 352 (4.55%)	15 / 350 (4.29%)
occurrences (all)	25	20	24
Upper respiratory tract infection			
subjects affected / exposed	36 / 345 (10.43%)	28 / 352 (7.95%)	36 / 350 (10.29%)
occurrences (all)	62	59	63
Urinary tract infection			
subjects affected / exposed	22 / 345 (6.38%)	17 / 352 (4.83%)	18 / 350 (5.14%)
occurrences (all)	30	22	22

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 July 2014	Amendment 1 (dated 17 July 2014) to the protocol was issued when 822 subjects were ongoing in the study. Changes to the protocol were considered to have no negative impact on the safety of subjects already enrolled into the study. These changes did not alter the study population, study design, or endpoints. The following major procedural changes (not all-inclusive) were made to the protocol: - Updates were made to the introduction and safety sections based on accumulating data with laquinimod and more stringent pregnancy prevention measures - In addition to the major revisions, this amended protocol included updates, modifications, and clarifications in sections related to stopping rules, disallowed medication, and study duration
25 February 2016	Amendment 2 was issued when 714 subjects were ongoing in the study. The primary purpose of this amendment was to introduce additional safety measures due to cardiovascular (CV) findings in other MS studies where higher doses of laquinimod (1.2 and 1.5 mg) were administered. These CV events resulted in the discontinuation of subjects treated with 1.2 and 1.5 mg from the respective studies in line with the Data Monitoring Committee (DMC) recommendations. The DMC also recommended that study subjects continuing on laquinimod 0.6 mg be reconsented with information about the CV risk seen in higher doses. The following major procedural changes (not all-inclusive) were made to the protocol: - All ongoing subjects were asked to reconsent to a revised form that included information on the CV risk findings at higher doses of laquinimod (1.2 and 1.5 mg). - Stopping rules were added for renal and hepatic impairment. - Glomerular filtration rate monitoring was to be performed at all visits, to assess renal function. - Extra emphasis was placed on moderate/strong inhibitors of cytochrome p450 (CYP)3A4 being disallowed. - Unscheduled urgent safety laboratory samples, PK blood samples, and/or samples for potential biomarker analyses may have been collected at the discretion of the Investigator or Medical Monitor at any time to assist with further investigations of CV events or other clinical event of interest. - A CV risk assessment and management procedure were added. - Ischemic cardiac events and cerebrovascular events are now classed as protocol-defined AEs for expedited reporting and were to be reported to the Sponsor within 48 hours, including completion of the corresponding dedicated CRF. - Subjects who were discontinued from study drug were encouraged to continue all scheduled visits and procedures until completion of the study (with the exception of procedures associated with drug dispensing and accountability, pregnancy testing, and GFR estimation).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported