Clinical trial results:
A Multinational, Multicenter, Open-Label, Single-Assignment Extension of the MS-LAQ-301 (ALLEGRO) 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	2009-012989-30
Trial protocol	GB NL EE ES HU DE CZ IT FR LT AT SE BG
Global end of trial date	01 July 2017

Results information

Result version number	v1 (current)
This version publication date	23 January 2019
First version publication date	23 January 2019

Trial information

Trial identification

Sponsor protocol code	MS-LAQ-301E

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00988052
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Teva Pharmaceutical Industries, Ltd
Sponsor organisation address	5 Bael 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	01 July 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 double-blind, placebo-controlled MS-LAQ-301 study and who completed the termination visit of this study according to the MS-LAQ-301 protocol, as long as the Sponsor continued the development of laquinimod 0.6 mg for 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 double-blind treatment phase in this subject population

Protection of trial subjects:

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

Written and/or oral information about the study was provided to all 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 patient.

This study included the following separate informed consent forms:
- a single informed consent form at the baseline visit
- an informed consent for patients who were permitted by the Sponsor to re-enroll in the study after study discontinuation due to a planned pregnancy (introduced by Global Protocol Amendment 2)
- additional informed consent forms for ancillary studies at the baseline visit (in selected countries/sites)
- magnetic resonance imaging (MRI) ancillary study
- magnetization transfer (MT) ancillary study
- magnetic resonance spectroscopy (MRS) ancillary study
- 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 3.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 November 2009
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	Austria: 5
Country: Number of subjects enrolled	Bulgaria: 81
Country: Number of subjects enrolled	Canada: 33
Country: Number of subjects enrolled	Czech Republic: 14
Country: Number of subjects enrolled	Germany: 99
Country: Number of subjects enrolled	Spain: 39
Country: Number of subjects enrolled	Estonia: 15
Country: Number of subjects enrolled	France: 24
Country: Number of subjects enrolled	United Kingdom: 18
Country: Number of subjects enrolled	Georgia: 22
Country: Number of subjects enrolled	Hungary: 25
Country: Number of subjects enrolled	Israel: 12
Country: Number of subjects enrolled	Italy: 35
Country: Number of subjects enrolled	Lithuania: 12
Country: Number of subjects enrolled	Netherlands: 7
Country: Number of subjects enrolled	Poland: 100
Country: Number of subjects enrolled	Romania: 23
Country: Number of subjects enrolled	Russian Federation: 86
Country: Number of subjects enrolled	Serbia: 20
Country: Number of subjects enrolled	Sweden: 11
Country: Number of subjects enrolled	Turkey: 1
Country: Number of subjects enrolled	Ukraine: 62
Country: Number of subjects enrolled	United States: 95
Worldwide total number of subjects	839
EEA total number of subjects	508

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)	839
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

In the preceding double-blind, placebo-controlled ALLEGRO study (study MS-LAQ-301), 1106 subjects with RRMS
were randomized to treatment, and 864 subjects completed the study according to the protocol (ie, by completing the ALLEGRO study termination visit procedures).

Pre-assignment

Screening details:

In this open-label extension study, 839 subjects with RRMS were enrolled to receive laquinimod 0.6 mg at 135 study sites in 22 countries by 135 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-301E 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-301 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 containing 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-301E 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-301 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 containing laquinimod 0.6 mg was taken orally at the same hour every day.

Number of subjects in period 1	Early laquinimod	Switch from placebo
Started	423	416
Completed	0	0
Not completed	423	416
Adverse event, serious fatal	1	3
Physician decision	27	28
Consent withdrawn by subject	90	91
Adverse event, non-fatal	35	28
Teva requested subject withdrawal	3	1
Pregnancy	6	6
Study terminated by sponsor	240	236
Lost to follow-up	6	11
Missing	1	-
Protocol deviation	6	5
Lack of efficacy	8	7

Baseline characteristics

Reporting groups	
Reporting group title	Early laquinimod
Reporting group description:	
All participants in MS-LAQ-301E 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-301 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-301E 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-301 double-blind study who were administered placebo daily for 24 months.	

Reporting group values	Early laquinimod	Switch from placebo	Total
Number of subjects	423	416	839
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)	423	416	839
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	41.1	40.5	
standard deviation	± 9.10	± 9.14	-
Sex: Female, Male Units: Subjects			
Female	298	271	569
Male	125	145	270
Race/Ethnicity, Customized Units: Subjects			
Asian / Oriental	2	0	2
Black / African American	1	5	6
Caucasian	414	401	815
Unknown	3	6	9
Other	2	2	4
Missing	1	2	3

End points

End points reporting groups

Reporting group title	Early laquinimod

Reporting group description:

All participants in MS-LAQ-301E 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-301 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-301E 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-301 double-blind study who were administered placebo daily 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 7.64 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		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	423	416		
Units: participants				
=>1 TEAE|	375	374		
=>1 Severe TEAE|	76	69		
=>1 TEAE of special interest|	109	105		
=>1 treatment-related TEAE|	139	153		
=>1 TEAE leading to death|	3	3		
=>1 Serious TEAE|	108	92		
=>1 TEAE causing discontinuation|	35	32		

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 low: <=45 and decrease >=30 beats/minute - Pulse rate high: >=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

End point type	Secondary

End point timeframe:

Day 1 up to 7.64 years

End point values	Early laquinimod	Switch from placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	423	416		
Units: participants				
Participants with at least one abnormality|	36	34		
Pulse rate - low|	1	1		
Pulse rate - high|	2	1		
Systolic blood pressure - low|	20	10		
Systolic blood pressure - high|	1	2		
Diastolic blood pressure - low|	7	7		
Diastolic blood pressure - high|	8	14		

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:

Day 1 up to 7.64 years

End point values	Early laquinimod	Switch from placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	422	415		
Units: participants				
ALT - change from Low / Non- PCS to High PCS|	8	14		
Albumen - change from High / Non-PCS to Low PCS|	1	0		
ALP - change from Low / Non- PCS to High PCS|	3	0		
p-Amylase - change from Low / Non-PCS to High PCS|	2	6		
AST - change from Low / Non- PCS to High PCS|	4	5		
CRP - change from Low / Non- PCS to High PCS|	41	51		
Calcium - change from High / Non-PCS to Low PCS|	1	4		
Calcium - change from Low / Non-PCS to High PCS|	1	2		
CK - change from Low / Non- PCS to High PCS|	16	17		
CTN - change from Low / Non- PCS to High PCS|	2	2		
FIB - change from Low / Non- PCS to High PCS|	37	38		
GGT - change from Low / Non- PCS to High PCS|	33	24		
Glucose - change from High / Non-PCS to Low PCS|	23	27		
Glucose - change from Low / Non-PCS to High PCS|	9	5		
Phosphate-change from High / Non-PCS to Low PCS|	14	15		
Phosphate-change from Low / Non-PCS to High PCS|	19	16		
K - change from High / Non- PCS to Low PCS|	4	3		
K - change from Low / Non- PCS to High PCS|	46	55		
Sodium - change from High / Non-PCS to Low PCS|	8	3		
Sodium - change from Low / Non-PCS to High PCS|	13	17		
Urea - change from Low / Non- PCS to High PCS|	3	4		

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:

Day 1 up to 7.64 years

End point values	Early laquinimod	Switch from placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	422	415		
Units: participants				
Hematocrit-change from High/Non-PCS to Low PCS|	36	29		
Hemoglobin-change from High/Non-PCS to Low PCS|	27	22		
Hemoglobin-change from Low/Non-PCS to High PCS|	0	1		
Leukocytes- change from High/Non-PCS to Low PCS|	1	1		
Leukocytes- change from Low/Non-PCS to High PCS|	4	3		
Neutrophils-change from High/Non-PCS to Low PCS|	15	12		
Platelets-change from High/Non-PCS to Low PCS|	4	7		
Platelets-change from Low/Non-PCS to High PCS|	2	6		

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:

Day 1 up to 7.64 years

End point values	Early laquinimod	Switch from placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	420	412		
Units: participants				
Normal / Normal|	189	198		
Normal / Abnormal, Not CS|	145	126		
Normal / Abnormal, CS|	2	3		
Abnormal, Not CS / Normal|	12	14		
Abnormal, Not CS / Abnormal, Not CS|	70	67		
Abnormal, Not CS / Abnormal, CS|	2	4		
Abnormal, CS / Normal|	0	0		
Abnormal, CS / Abnormal, Not CS|	0	0		
Abnormal, CS / Abnormal, CS|	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 up to 7.64 years

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Switch from Placebo to Laquinimod 0.6 mg

Reporting group description:

All participants in MS-LAQ-301E 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-301 double-blind study who were administered placebo daily for 24 months.

Reporting group title	Early Laquinimod 0.6 mg

Reporting group description:

All participants in MS-LAQ-301E 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-301 double-blind study who were administered laquinimod 0.6 mg daily for 24 months.

Serious adverse events	Switch from Placebo to Laquinimod 0.6 mg	Early Laquinimod 0.6 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	92 / 416 (22.12%)	108 / 423 (25.53%)	
number of deaths (all causes)	3	3	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Anogenital warts			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
B-cell lymphoma			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			

subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign neoplasm of thyroid gland			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign ovarian tumour			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	1 / 416 (0.24%)	2 / 423 (0.47%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer stage II			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervix carcinoma stage 0			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic lymphocytic leukaemia stage 1			
subjects affected / exposed	1 / 416 (0.24%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibroadenoma of breast			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hodgkin's disease			

subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraductal proliferative breast lesion			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive breast carcinoma			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Keratoacanthoma			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Langerhans' cell histiocytosis			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma metastatic			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastases to central nervous system			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastases to lung			

subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oncocytoma			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian adenoma			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cancer metastatic			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papillary thyroid cancer			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cancer			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small cell lung cancer metastatic			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubular breast carcinoma			

subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	4 / 416 (0.96%)	3 / 423 (0.71%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulval cancer			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	2 / 416 (0.48%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery stenosis			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			

Cholecystectomy			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hysterectomy			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc operation			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Knee arthroplasty			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrectomy			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fusion surgery			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	3 / 416 (0.72%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	1 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			

subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest discomfort			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 416 (0.00%)	2 / 423 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Drowning			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Fatigue			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait disturbance			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired healing			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inflammation			

subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza like illness			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device pain			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Acquired hydrocele			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Endometrial hyperplasia			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometriosis			
subjects affected / exposed	2 / 416 (0.48%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibrocystic breast disease			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrosalpinx			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Menometrorrhagia			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metrorrhagia			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst			
subjects affected / exposed	1 / 416 (0.24%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine polyp			
subjects affected / exposed	1 / 416 (0.24%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine prolapse			

subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal prolapse			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiectasis			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis chronic			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 416 (0.00%)	2 / 423 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal polyps			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal septum deviation			
subjects affected / exposed	0 / 416 (0.00%)	2 / 423 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal polyp			

subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 416 (0.24%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 416 (0.24%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Agoraphobia			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Completed suicide			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Depression			

subjects affected / exposed	2 / 416 (0.48%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Mood disorder due to a general medical condition			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurosis			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panic disorder			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Substance-induced psychotic disorder			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
C-reactive protein increased			
subjects affected / exposed	1 / 416 (0.24%)	4 / 423 (0.95%)	
occurrences causally related to treatment / all	0 / 1	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hepatic enzyme increased			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain contusion			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Comminuted fracture			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial bones fracture			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 416 (0.00%)	6 / 423 (1.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 416 (0.00%)	2 / 423 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Foot fracture			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound complication			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural complication			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			

subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	2 / 416 (0.48%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seroma			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skull fracture			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	1 / 416 (0.24%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 416 (0.24%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute myocardial infarction			
subjects affected / exposed	1 / 416 (0.24%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			

subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	2 / 416 (0.48%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 416 (0.00%)	2 / 423 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	1 / 416 (0.24%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	2 / 416 (0.48%)	2 / 423 (0.47%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			

subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Silent myocardial infarction			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular extrasystoles			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carpal tunnel syndrome			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral artery occlusion			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			

subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervicobrachial syndrome			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 416 (0.00%)	3 / 423 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 416 (0.24%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar radiculopathy			

subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple sclerosis relapse			
subjects affected / exposed	2 / 416 (0.48%)	3 / 423 (0.71%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Optic neuritis			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Simple partial seizures			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 416 (0.24%)	3 / 423 (0.71%)	
occurrences causally related to treatment / all	0 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trigeminal neuralgia			

subjects affected / exposed	1 / 416 (0.24%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 416 (0.24%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow oedema			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenitis			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Blindness unilateral			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye haemorrhage			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Uveitis			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal adhesions			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal hernia			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 416 (0.24%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 416 (0.24%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			

subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 416 (0.48%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiatus hernia			
subjects affected / exposed	0 / 416 (0.00%)	2 / 423 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 416 (0.24%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Irritable bowel syndrome			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Omental infarction			

subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis chronic			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Volvulus			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary colic			

subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 416 (0.24%)	2 / 423 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestasis			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocholecystis			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Hidradenitis			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Bladder dysfunction			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus urinary			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	2 / 416 (0.48%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ketonuria			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 416 (0.24%)	2 / 423 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral meatus stenosis			

subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral stenosis			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary incontinence			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperparathyroidism primary			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parathyroid gland enlargement			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 416 (0.24%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Arthritis			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical spinal stenosis			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin pain			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	3 / 416 (0.72%)	2 / 423 (0.47%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc space narrowing			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint hyperextension			

subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint instability			
subjects affected / exposed	0 / 416 (0.00%)	2 / 423 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Knee impingement syndrome			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	2 / 416 (0.48%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteochondrosis			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	1 / 416 (0.24%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudarthrosis			

subjects affected / exposed	1 / 416 (0.24%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatoid arthritis			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondylolisthesis			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon calcification			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute sinusitis			

subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	3 / 416 (0.72%)	4 / 423 (0.95%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
subjects affected / exposed	1 / 416 (0.24%)	2 / 423 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bartholin's abscess			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast abscess			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 416 (0.24%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis infective			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic tonsillitis			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			

subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Furuncle			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin abscess			
subjects affected / exposed	0 / 416 (0.00%)	2 / 423 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic echinococciasis			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Latent syphilis			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Latent tuberculosis			

subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis viral			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mycotoxicosis			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media chronic			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian abscess			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 416 (0.00%)	4 / 423 (0.95%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periumbilical abscess			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pertussis			

subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal abscess			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pilonidal cyst			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 416 (0.72%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	1 / 416 (0.24%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis chronic			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salpingo-oophoritis			

subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubo-ovarian abscess			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 416 (0.24%)	2 / 423 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vestibular neuronitis			
subjects affected / exposed	1 / 416 (0.24%)	0 / 423 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetic ketoacidosis			

subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obesity			
subjects affected / exposed	0 / 416 (0.00%)	1 / 423 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Switch from Placebo to Laquinimod 0.6 mg	Early Laquinimod 0.6 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	300 / 416 (72.12%)	299 / 423 (70.69%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	22 / 416 (5.29%)	13 / 423 (3.07%)	
occurrences (all)	27	16	
C-reactive protein increased			
subjects affected / exposed	31 / 416 (7.45%)	26 / 423 (6.15%)	
occurrences (all)	37	31	
Gamma-glutamyltransferase increased			
subjects affected / exposed	16 / 416 (3.85%)	22 / 423 (5.20%)	
occurrences (all)	23	27	
Injury, poisoning and procedural complications			

Fall			
subjects affected / exposed	23 / 416 (5.53%)	20 / 423 (4.73%)	
occurrences (all)	30	30	
Vascular disorders			
Hypertension			
subjects affected / exposed	26 / 416 (6.25%)	32 / 423 (7.57%)	
occurrences (all)	26	32	
Nervous system disorders			
Headache			
subjects affected / exposed	86 / 416 (20.67%)	57 / 423 (13.48%)	
occurrences (all)	160	132	
Multiple sclerosis relapse			
subjects affected / exposed	29 / 416 (6.97%)	17 / 423 (4.02%)	
occurrences (all)	36	35	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	16 / 416 (3.85%)	22 / 423 (5.20%)	
occurrences (all)	17	25	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	31 / 416 (7.45%)	25 / 423 (5.91%)	
occurrences (all)	38	30	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	31 / 416 (7.45%)	19 / 423 (4.49%)	
occurrences (all)	39	23	
Diarrhoea			
subjects affected / exposed	21 / 416 (5.05%)	24 / 423 (5.67%)	
occurrences (all)	23	31	
Nausea			
subjects affected / exposed	26 / 416 (6.25%)	24 / 423 (5.67%)	
occurrences (all)	37	27	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	35 / 416 (8.41%)	24 / 423 (5.67%)	
occurrences (all)	40	26	
Psychiatric disorders			

Depression			
subjects affected / exposed	28 / 416 (6.73%)	35 / 423 (8.27%)	
occurrences (all)	35	41	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	47 / 416 (11.30%)	41 / 423 (9.69%)	
occurrences (all)	59	57	
Back pain			
subjects affected / exposed	77 / 416 (18.51%)	78 / 423 (18.44%)	
occurrences (all)	124	127	
Musculoskeletal pain			
subjects affected / exposed	25 / 416 (6.01%)	11 / 423 (2.60%)	
occurrences (all)	29	15	
Pain in extremity			
subjects affected / exposed	33 / 416 (7.93%)	28 / 423 (6.62%)	
occurrences (all)	45	35	
Infections and infestations			
Bronchitis			
subjects affected / exposed	33 / 416 (7.93%)	33 / 423 (7.80%)	
occurrences (all)	46	44	
Influenza			
subjects affected / exposed	34 / 416 (8.17%)	28 / 423 (6.62%)	
occurrences (all)	46	41	
Nasopharyngitis			
subjects affected / exposed	112 / 416 (26.92%)	106 / 423 (25.06%)	
occurrences (all)	210	169	
Sinusitis			
subjects affected / exposed	28 / 416 (6.73%)	27 / 423 (6.38%)	
occurrences (all)	47	36	
Upper respiratory tract infection			
subjects affected / exposed	41 / 416 (9.86%)	43 / 423 (10.17%)	
occurrences (all)	65	69	
Urinary tract infection			
subjects affected / exposed	39 / 416 (9.38%)	55 / 423 (13.00%)	
occurrences (all)	76	110	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 November 2009	Amendment 1 (dated 01 November 2009) to the protocol was issued before any subjects were enrolled into the study. The amendment was aimed to modify the protocol according to the Food and Drug Administration (FDA) Guidance for Industry on the issue of Drug-Induced Liver Injury: Premarketing Clinical Evaluation. The following major procedural changes (not all-inclusive) were made to the protocol: - Modification of the "Guidance for Safety Monitoring" (Appendix 6) adopting the principles of the FDA Guideline titled "Drug-Induced Liver Injury: Premarketing Clinical Evaluation" (July, 2009) - Clarification of the sequence of administration of questionnaires and the Multiple Sclerosis Functional Composite assessment at each visit - Modification of the MRI outcome of brain volume change in light of technical capabilities of the equipment
17 July 2014	Amendment 2 (dated 17 July 2014) to the protocol was issued when 639 subjects were ongoing in this study. Changes to the protocol were considered to have no negative impact on the safety of subjects ongoing in this 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 3 (dated 25 February 2016) to the protocol was issued when 542 subjects were ongoing in this 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. The DMC 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 re-consent to a revised form that includes information on the CV risk findings at higher doses of laquinimod (1.2 mg and 1.5 mg). - Stopping rules were added for renal and hepatic impairment. - Glomerular filtration rate and weight were 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, pharmacokinetic blood samples, and/or samples for potential biomarker analyses may have been collected at the discretion of the Investigator 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 were classed as protocol-defined adverse events for expedited reporting and were to be reported to the Sponsor within 48 hours. - Subjects who were discontinued from study drug were encouraged to continue all scheduled visits and procedures until completion of the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported