Clinical trial results:
A Phase 3, Double-Blind, Randomized, Long-Term, Placebo-Controlled, Multicenter Study Evaluating the Safety and Efficacy of Obeticholic Acid in Subjects with Nonalcoholic Steatohepatitis

Summary

EudraCT number	2015-002560-16
Trial protocol	GB DE AT SE BE DK ES FI PT HU PL
Global end of trial date	15 November 2023

Results information

Result version number	v1 (current)
This version publication date	14 September 2024
First version publication date	14 September 2024

Trial information

Trial identification

Sponsor protocol code	747-303

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02548351
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Intercept Pharmaceuticals, Inc.
Sponsor organisation address	305 Madison Avenue, Morristown, New Jersey, United States, 07960
Public contact	Medical Information, Intercept Pharmaceuticals, Inc., +1 8447824278, medinfo@interceptpharma.com
Scientific contact	Medical Information, Intercept Pharmaceuticals, Inc., +1 8447824278, medinfo@interceptpharma.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 September 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 September 2023
Global end of trial reached?	Yes
Global end of trial date	15 November 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Primary objective assessed of the trial were:
To evaluate the effect of OCA compared to placebo on all-cause mortality and liverrelated clinical outcomes as measured by the time to first occurrence of any of the following adjudicated events (clinical outcomes composite endpoint):
Death (all cause)
Model of end stage liver disease (MELD) score ≥15
Liver transplant
Hospitalization (as defined by a stay of ≥24 hours) for onset of:
Variceal bleed
Hepatic encephalopathy (as defined by a West Haven score of ≥2)
Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
Ascites secondary to cirrhosis and requiring medical intervention (eg, diuretics or paracentesis)
Progression to cirrhosis

Protection of trial subjects:

Not Applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 September 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 16
Country: Number of subjects enrolled	Portugal: 13
Country: Number of subjects enrolled	Spain: 81
Country: Number of subjects enrolled	Sweden: 11
Country: Number of subjects enrolled	United Kingdom: 112
Country: Number of subjects enrolled	Austria: 10
Country: Number of subjects enrolled	Belgium: 29
Country: Number of subjects enrolled	Denmark: 24
Country: Number of subjects enrolled	Finland: 16
Country: Number of subjects enrolled	France: 126
Country: Number of subjects enrolled	Germany: 75
Country: Number of subjects enrolled	Hungary: 11
Country: Number of subjects enrolled	Italy: 71
Country: Number of subjects enrolled	Australia: 69

Country: Number of subjects enrolled	Canada: 92
Country: Number of subjects enrolled	Switzerland: 21
Country: Number of subjects enrolled	Israel: 31
Country: Number of subjects enrolled	New Zealand: 20
Country: Number of subjects enrolled	Serbia: 6
Country: Number of subjects enrolled	United States: 1643
Worldwide total number of subjects	2477
EEA total number of subjects	483

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)	1961
From 65 to 84 years	516
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a phase 3, double-blind, randomized, long-term, placebo-controlled, multicenter study evaluating the safety and efficacy of Obeticholic Acid (OCA) in Participants with Nonalcoholic Steatohepatitis (NASH).

Pre-assignment

Screening details:

The study was conducted at approximately 350 investigational sites globally.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	OCA 10 Milligrams (mg)

Arm description:

Participants were randomized to receive OCA 10 mg once daily orally with water.

Arm type	Experimental
Investigational medicinal product name	OCA 10 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants were administered with OCA 10 mg tablets with water.

Arm title	OCA 25 mg

Arm description:

Participants were randomized to receive OCA 25 mg once daily orally with water.

Arm type	Experimental
Investigational medicinal product name	OCA 25 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants were administered with OCA 25 mg tablets with water.

Arm title	Placebo

Arm description:

Participants were randomized to receive matching placebo once daily orally with water.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants were administered with matching placebo orally with water.

Number of subjects in period 1	OCA 10 Milligrams (mg)	OCA 25 mg	Placebo
Started	825	827	825
Completed	0	0	0
Not completed	825	827	825
Site Closure	14	5	7
Adverse event, serious fatal	11	15	12
Consent withdrawn by subject	149	154	152
Non-compliance with Study Drug	4	2	-
Physician decision	11	18	11
Study terminated by Sponsor	549	509	528
Adverse event, non-fatal	22	56	36
Unspecified	19	16	20
Lost to follow-up	43	50	57
Missing	1	1	-
Protocol deviation	2	1	2

Baseline characteristics

Reporting groups	
Reporting group title	OCA 10 Milligrams (mg)
Reporting group description:	
Participants were randomized to receive OCA 10 mg once daily orally with water.	
Reporting group title	OCA 25 mg
Reporting group description:	
Participants were randomized to receive OCA 25 mg once daily orally with water.	
Reporting group title	Placebo
Reporting group description:	
Participants were randomized to receive matching placebo once daily orally with water.	

Reporting group values	OCA 10 Milligrams (mg)	OCA 25 mg	Placebo
Number of subjects	825	827	825
Age categorical Units: Subjects			
Adults (18-64 years)	655	643	663
From 65-84 years	170	184	162
Age continuous Units: years			
arithmetic mean	55.3	55.3	54.4
standard deviation	± 10.76	± 11.71	± 11.21
Gender categorical Units: Subjects			
Female	475	494	347
Male	350	333	478

Reporting group values	Total		
Number of subjects	2477		
Age categorical Units: Subjects			
Adults (18-64 years)	1961		
From 65-84 years	516		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	1316		
Male	1161		

End points

End points reporting groups

Reporting group title	OCA 10 Milligrams (mg)
Reporting group description:	
Participants were randomized to receive OCA 10 mg once daily orally with water.	
Reporting group title	OCA 25 mg
Reporting group description:	
Participants were randomized to receive OCA 25 mg once daily orally with water.	
Reporting group title	Placebo
Reporting group description:	
Participants were randomized to receive matching placebo once daily orally with water.	

Primary: Time to the First Adjudicated Event for Clinical Outcome Composite Endpoint: Percentage of Participants With an Event

End point title	Time to the First Adjudicated Event for Clinical Outcome Composite Endpoint: Percentage of Participants With an Event
End point description:	
All potential liver-related clinical outcomes that occurred after administration of first dose of investigational product were reviewed and adjudicated by blinded, independent Hepatic Outcomes Committee (HOC). Adjudicated results were used to assess effect of OCA, compared to placebo in conjunction with established local standard of care, on clinical outcomes in participants with NASH as measured by time to first occurrence of any of following adjudicated events, derived as a composite event endpoint of death (all-cause), liver transplant, MELD ≥15 Score, hospitalization (defined by a stay of 24 hours or greater) for onset of: variceal bleed, hepatic encephalopathy (defined by a West Haven score of ≥2), and spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis), ascites secondary to cirrhosis requiring medical intervention, and histological progression to Cirrhosis. Clinical events distribution was estimated using Kaplan-Meier methodology.	
End point type	Primary
End point timeframe:	
Up to 7 years	

End point values	OCA 10 Milligrams (mg)	OCA 25 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	729	730	728	
Units: Percentage of participants with event				
number (confidence interval 95%)	15.8 (13.2 to 18.6)	14.7 (12.2 to 17.4)	18.8 (16.0 to 21.9)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	OCA 10 Milligrams (mg) v Placebo

Number of subjects included in analysis	1457
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1028
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.814
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.635
upper limit	1.043

Statistical analysis title	Statistical Analysis 2
Comparison groups	OCA 25 mg v Placebo
Number of subjects included in analysis	1458
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0444
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.772
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	0.994

Secondary: Percentage of Responders With Improvement of Fibrosis by at Least One Stage With no Worsening of NASH Using Consensus Read Method of Scheduled Liver Biopsies

End point title	Percentage of Responders With Improvement of Fibrosis by at Least One Stage With no Worsening of NASH Using Consensus Read Method of Scheduled Liver Biopsies

End point description:

Fibrosis stage was evaluated by NASH Clinical Research Network (CRN) Fibrosis Staging System as follows: Stage 0: No fibrosis, Stage 1: Perisinusoidal/periportal fibrosis, Stage 1A: Mild, zone 3, perisinusoidal fibrosis, Stage 1B: Moderate, zone 3, perisinusoidal fibrosis, Stage 1C: Portal/periportal fibrosis, Stage 2: Perisinusoidal and portal/periportal fibrosis, Stage 3: Bridging fibrosis and Stage 4: Cirrhosis. No worsening of NASH was defined as no worsening of hepatocellular ballooning, no worsening of lobular inflammation, and no worsening of steatosis. Responders are defined as participants who did not discontinue treatment due to Adverse event (AE) or did not die and had evaluable post-Baseline biopsy assessment. Mantel-Haenszel method is used to construct the confidence intervals. Intent-to-Treat (ITT) Population comprised of all randomized participants with fibrosis stage 2 or stage 3 who receive at least 1 dose of investigational product.

End point type	Secondary

End point timeframe:

Up to 7 years

End point values	OCA 10 Milligrams (mg)	OCA 25 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	729	730	728	
Units: Percentage of participants				
number (not applicable)	17.1	19.5	10.0	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	OCA 10 Milligrams (mg) v Placebo
Number of subjects included in analysis	1457
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment difference
Point estimate	7.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.6
upper limit	10.6

Statistical analysis title	Statistical Analysis 2
Comparison groups	OCA 25 mg v Placebo
Number of subjects included in analysis	1458
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment difference
Point estimate	9.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.8
upper limit	13

Secondary: Percentage of Participants Who Showed Improvement in Fibrosis by at

Least 1 Stage and/or Resolution of NASH Without Worsening of Either Using Consensus Read Method

End point title	Percentage of Participants Who Showed Improvement in Fibrosis by at Least 1 Stage and/or Resolution of NASH Without Worsening of Either Using Consensus Read Method

End point description:

Fibrosis stage was evaluated by NASH Clinical Research Network (CRN) Fibrosis Staging System as follows: Stage 0: No fibrosis, Stage 1: Perisinusoidal/periportal fibrosis, Stage 1A: Mild, zone 3, perisinusoidal fibrosis, Stage 1B: Moderate, zone3, perisinusoidal fibrosis, Stage 1C: Portal/periportal fibrosis, Stage 2: Perisinusoidal and portal/periportal fibrosis, Stage 3: Bridging fibrosis and Stage 4: Cirrhosis. Resolution of NASH is defined as absence of fatty liver disease, or presence of simple or isolated steatosis without steatohepatitis, with a NAS (NAFLD Activity Score) of 0 for ballooning and 0-1 for inflammation. NAS ranges from 0-12; 0: no features of fatty liver disease and 12: highest degree of fatty liver disease. Higher scores signify worse symptoms. Responders are who did not discontinue treatment due to Adverse event (AE) or did not die and had evaluable post-Baseline biopsy assessment. Mantel-Haenszel method is used to construct confidence intervals

End point type	Secondary

End point timeframe:

Up to 7 years

End point values	OCA 10 Milligrams (mg)	OCA 25 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	729	730	728	
Units: Percentage of participants				
number (not applicable)	18.5	20.8	11.8	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	OCA 10 Milligrams (mg) v Placebo
Number of subjects included in analysis	1457
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0004
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment difference
Point estimate	6.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	3
upper limit	10.4

Statistical analysis title	Statistical Analysis 2
Comparison groups	OCA 25 mg v Placebo

Number of subjects included in analysis	1458
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment difference
Point estimate	9
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.2
upper limit	12.8

Secondary: Number of Participants With Treatment Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

End point title	Number of Participants With Treatment Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

End point description:

An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. A TEAE was defined as any AE that either newly appeared, increased in frequency, or worsened in severity following treatment up to 30 days from last dose of permanent investigational product discontinuation. Serious AE (SAE) was defined as any AE resulting in death, immediate risk of death, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity, or a congenital/anomaly/birth defect, or any other medically important event. Safety Population comprised all randomized participants, all fibrosis stages, who receive at least 1 dose of investigational product (OCA or placebo).

End point type	Secondary

End point timeframe:

Up to 7 years

End point values	OCA 10 Milligrams (mg)	OCA 25 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	825	827	825	
Units: Participants				
number (not applicable)				
TEAEs	798	813	781	
SAEs	273	276	248	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 7 years

Adverse event reporting additional description:

Treatment emergent adverse events and serious adverse events were collected in the Safety Population. Safety Population comprises of participants who received at least one dose of study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	OCA 10 Milligrams (mg)

Reporting group description:

Participants were randomized to receive OCA 10 mg once daily orally with water.

Reporting group title	OCA 25 mg

Reporting group description:

Participants were randomized to receive OCA 25 mg once daily orally with water.

Reporting group title	Placebo

Reporting group description: -

Serious adverse events	OCA 10 Milligrams (mg)	OCA 25 mg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	273 / 825 (33.09%)	276 / 827 (33.37%)	248 / 825 (30.06%)
number of deaths (all causes)	14	19	14
number of deaths resulting from adverse events	14	19	14
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of salivary gland			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal squamous cell carcinoma			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			

subjects affected / exposed	2 / 825 (0.24%)	0 / 827 (0.00%)	0 / 825 (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
Benign hepatic neoplasm			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign neoplasm of spinal cord			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign salivary gland neoplasm			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Bladder transitional cell carcinoma			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder transitional cell carcinoma recurrent			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone cancer			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain neoplasm			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			

subjects affected / exposed	4 / 825 (0.48%)	2 / 827 (0.24%)	4 / 825 (0.48%)
occurrences causally related to treatment / all	0 / 4	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer metastatic			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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 recurrent			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangiocarcinoma			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic lymphocytic leukaemia			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic myeloid leukaemia			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clear cell renal cell carcinoma			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Colon adenoma			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer			

subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diffuse large B-cell lymphoma			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	3 / 825 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial adenocarcinoma			
subjects affected / exposed	2 / 825 (0.24%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial cancer			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial cancer metastatic			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
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 stromal tumour			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glioblastoma			
subjects affected / exposed	1 / 825 (0.12%)	1 / 827 (0.12%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemangiopericytoma			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic cancer			

subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Hepatic neoplasm			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatocellular carcinoma			
subjects affected / exposed	8 / 825 (0.97%)	6 / 827 (0.73%)	3 / 825 (0.36%)
occurrences causally related to treatment / all	1 / 8	0 / 9	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intraductal papillary mucinous neoplasm			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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 papilloma of breast			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intraductal proliferative breast lesion			
subjects affected / exposed	2 / 825 (0.24%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive breast carcinoma			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive ductal breast carcinoma			
subjects affected / exposed	5 / 825 (0.61%)	0 / 827 (0.00%)	2 / 825 (0.24%)
occurrences causally related to treatment / all	0 / 6	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine benign neoplasm			

subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lip and/or oral cavity cancer			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
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 adenocarcinoma			
subjects affected / exposed	2 / 825 (0.24%)	2 / 827 (0.24%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Lung neoplasm			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Lung neoplasm malignant			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Lymphoma			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma			
subjects affected / exposed	2 / 825 (0.24%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant pleural effusion			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Metastases to bone			

subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Metastases to central nervous system			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Metastases to skin			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Neoplasm malignant			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuroendocrine tumour			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal carcinoma			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Oral papilloma			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Papillary thyroid cancer			
subjects affected / exposed	1 / 825 (0.12%)	2 / 827 (0.24%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parathyroid tumour benign			

subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Phaeochromocytoma			
subjects affected / exposed	0 / 825 (0.00%)	2 / 827 (0.24%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Plasma cell myeloma			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleomorphic adenoma			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	5 / 825 (0.61%)	4 / 827 (0.48%)	2 / 825 (0.24%)
occurrences causally related to treatment / all	0 / 5	0 / 4	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer metastatic			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer recurrent			
subjects affected / exposed	0 / 825 (0.00%)	2 / 827 (0.24%)	2 / 825 (0.24%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer stage II			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal cancer			

subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
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 cancer			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cell carcinoma			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal neoplasm			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small cell lung cancer			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Squamous cell carcinoma			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of lung			
subjects affected / exposed	0 / 825 (0.00%)	2 / 827 (0.24%)	0 / 825 (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
Thyroid cancer			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tongue neoplasm malignant stage unspecified			

subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transitional cell carcinoma			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	2 / 825 (0.24%)
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 leiomyosarcoma			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
PNEUMONIA METASTASIS OF OESOPHAGEAL CANCER			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Vascular disorders			
Aortic dissection			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic stenosis			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	2 / 825 (0.24%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arterial haemorrhage			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arterial occlusive disease			

subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Arteriosclerosis			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Deep vein thrombosis			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (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
Hypertension			
subjects affected / exposed	2 / 825 (0.24%)	2 / 827 (0.24%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	2 / 825 (0.24%)	0 / 827 (0.00%)	2 / 825 (0.24%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive emergency			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Hypotension			
subjects affected / exposed	2 / 825 (0.24%)	3 / 827 (0.36%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	1 / 825 (0.12%)	1 / 827 (0.12%)	0 / 825 (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
Peripheral arterial occlusive disease			

subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Shock haemorrhagic			
subjects affected / exposed	0 / 825 (0.00%)	2 / 827 (0.24%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Varicose vein			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
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			
Liver transplant			
subjects affected / exposed	2 / 825 (0.24%)	1 / 827 (0.12%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Physiotherapy			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotator cuff repair			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

General disorders and administration site conditions			
Hiatus hernia			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adverse drug reaction			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	2 / 825 (0.24%)	2 / 827 (0.24%)	2 / 825 (0.24%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast complication associated with device			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Calcinosis			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest discomfort			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	5 / 825 (0.61%)	8 / 827 (0.97%)	6 / 825 (0.73%)
occurrences causally related to treatment / all	0 / 5	1 / 8	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 825 (0.00%)	2 / 827 (0.24%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Device deployment issue			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Device dislocation			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disease progression			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysplasia			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impaired healing			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mass			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
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-cardiac chest pain			
subjects affected / exposed	3 / 825 (0.36%)	7 / 827 (0.85%)	2 / 825 (0.24%)
occurrences causally related to treatment / all	0 / 3	0 / 7	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			

subjects affected / exposed	0 / 825 (0.00%)	3 / 827 (0.36%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 825 (0.00%)	2 / 827 (0.24%)	0 / 825 (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
Vascular stent occlusion			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug hypersensitivity			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypersensitivity			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
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	4 / 825 (0.48%)	4 / 827 (0.48%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 4	0 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	3 / 825 (0.36%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Breast haematoma			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Endometrial hyperplasia			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Endometrial thickening			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Menorrhagia			
subjects affected / exposed	1 / 825 (0.12%)	1 / 827 (0.12%)	0 / 825 (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
Metrorrhagia			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic congestion			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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 pain			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic prolapse			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectocele			

subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine polyp			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (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
Uterine prolapse			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterovaginal prolapse			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	2 / 825 (0.24%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	0 / 825 (0.00%)	2 / 827 (0.24%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Asthma			
subjects affected / exposed	1 / 825 (0.12%)	5 / 827 (0.60%)	2 / 825 (0.24%)
occurrences causally related to treatment / all	0 / 1	0 / 5	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma-chronic obstructive pulmonary disease overlap syndrome			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atelectasis			

subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopneumopathy			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	5 / 825 (0.61%)	3 / 827 (0.36%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 7	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	3 / 825 (0.36%)	5 / 827 (0.60%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Dyspnoea exertional			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Haemothorax			
subjects affected / exposed	1 / 825 (0.12%)	1 / 827 (0.12%)	0 / 825 (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
Hypoxia			

subjects affected / exposed	1 / 825 (0.12%)	1 / 827 (0.12%)	0 / 825 (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
Idiopathic pulmonary fibrosis			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Interstitial lung disease			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasopharyngeal polyp			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Organising pneumonia			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Pneumonia aspiration			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax spontaneous			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary alveolar haemorrhage			

subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	3 / 825 (0.36%)	1 / 827 (0.12%)	2 / 825 (0.24%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary fibrosis			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (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
Pulmonary hilum mass			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary mass			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	2 / 825 (0.24%)	1 / 827 (0.12%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Adjustment disorder with depressed mood			

subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Bipolar I disorder			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	2 / 825 (0.24%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bipolar disorder			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Completed suicide			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	2 / 825 (0.24%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 2
Confusional state			
subjects affected / exposed	0 / 825 (0.00%)	2 / 827 (0.24%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	3 / 825 (0.36%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Major depression			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	2 / 825 (0.24%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental disorder			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			

subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Panic disorder			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychogenic seizure			
subjects affected / exposed	1 / 825 (0.12%)	1 / 827 (0.12%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychogenic tremor			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rapid eye movements sleep abnormal			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Suicidal ideation			
subjects affected / exposed	0 / 825 (0.00%)	2 / 827 (0.24%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ANXIETY-DEPRESSIVE DISORDER			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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			
Acute hepatic failure			

subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autoimmune hepatitis			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (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
Bile duct obstruction			
subjects affected / exposed	1 / 825 (0.12%)	1 / 827 (0.12%)	0 / 825 (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
Bile duct stone			
subjects affected / exposed	3 / 825 (0.36%)	3 / 827 (0.36%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	2 / 3	0 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary colic			
subjects affected / exposed	0 / 825 (0.00%)	2 / 827 (0.24%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary tract disorder			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Biloma			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Cholangitis			
subjects affected / exposed	0 / 825 (0.00%)	2 / 827 (0.24%)	0 / 825 (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
Cholangitis acute			

subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Cholecystitis			
subjects affected / exposed	2 / 825 (0.24%)	4 / 827 (0.48%)	4 / 825 (0.48%)
occurrences causally related to treatment / all	0 / 2	2 / 4	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	2 / 825 (0.24%)	9 / 827 (1.09%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	2 / 2	1 / 9	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis chronic			
subjects affected / exposed	1 / 825 (0.12%)	2 / 827 (0.24%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	4 / 825 (0.48%)	8 / 827 (0.97%)	4 / 825 (0.48%)
occurrences causally related to treatment / all	3 / 4	2 / 8	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholestasis			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholestatic liver injury			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (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
Chronic hepatic failure			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug-induced liver injury			

subjects affected / exposed	0 / 825 (0.00%)	3 / 827 (0.36%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder perforation			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder polyp			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic cirrhosis			
subjects affected / exposed	0 / 825 (0.00%)	2 / 827 (0.24%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	1 / 825 (0.12%)	1 / 827 (0.12%)	0 / 825 (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
Hepatic haematoma			
subjects affected / exposed	3 / 825 (0.36%)	2 / 827 (0.24%)	2 / 825 (0.24%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic lesion			
subjects affected / exposed	2 / 825 (0.24%)	0 / 827 (0.00%)	0 / 825 (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
Hepatitis			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (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
Hepatorenal syndrome			

subjects affected / exposed	1 / 825 (0.12%)	1 / 827 (0.12%)	0 / 825 (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
Hyperbilirubinaemia			
subjects affected / exposed	1 / 825 (0.12%)	2 / 827 (0.24%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperplastic cholecystopathy			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (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
Investigations			
Arthroscopy			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	1 / 825 (0.12%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronavirus test positive			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Fibrin D dimer increased			

subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoglobin decreased			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Human rhinovirus test positive			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver function test abnormal			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Red blood cell sedimentation rate increased			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Troponin increased			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight increased			

subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 825 (0.12%)	1 / 827 (0.12%)	0 / 825 (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
Alcohol poisoning			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaesthetic complication pulmonary			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Ankle fracture			
subjects affected / exposed	0 / 825 (0.00%)	3 / 827 (0.36%)	3 / 825 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical vertebral fracture			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest injury			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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	0 / 825 (0.00%)	1 / 827 (0.12%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Craniocerebral injury			

subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial bones fracture			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Fall			
subjects affected / exposed	3 / 825 (0.36%)	3 / 827 (0.36%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fibula fracture			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot fracture			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Head injury			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			

subjects affected / exposed	2 / 825 (0.24%)	1 / 827 (0.12%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 825 (0.00%)	2 / 827 (0.24%)	4 / 825 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incarcerated incisional hernia			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Incisional hernia			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Intentional overdose			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Joint injury			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laceration			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar vertebral fracture			

subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscus injury			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	2 / 825 (0.24%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Near drowning			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Overdose			
subjects affected / exposed	2 / 825 (0.24%)	0 / 827 (0.00%)	0 / 825 (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
Patella fracture			
subjects affected / exposed	2 / 825 (0.24%)	0 / 827 (0.00%)	0 / 825 (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
Pelvic fracture			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngeal injury			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural complication			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	3 / 825 (0.36%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural discomfort			

subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haematoma			
subjects affected / exposed	5 / 825 (0.61%)	3 / 827 (0.36%)	2 / 825 (0.24%)
occurrences causally related to treatment / all	0 / 5	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	1 / 825 (0.12%)	4 / 827 (0.48%)	2 / 825 (0.24%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural inflammation			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Procedural intestinal perforation			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural pain			
subjects affected / exposed	4 / 825 (0.48%)	6 / 827 (0.73%)	4 / 825 (0.48%)
occurrences causally related to treatment / all	0 / 4	0 / 6	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	1 / 825 (0.12%)	2 / 827 (0.24%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	1 / 825 (0.12%)	1 / 827 (0.12%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seroma			

subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Shunt malfunction			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Skin graft failure			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal column injury			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord injury cervical			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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 fracture			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	2 / 825 (0.24%)	0 / 827 (0.00%)	0 / 825 (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
Tendon rupture			

subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thoracic vertebral fracture			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	0 / 825 (0.00%)	2 / 827 (0.24%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic haematoma			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Upper limb fracture			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention postoperative			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
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 secretion			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
INTRACRANIAL HEMORRHAGE			

subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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			
Arnold-Chiari malformation			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Arteriovenous malformation			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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 cerebrovascular anomaly			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rathke's cleft cyst			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
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 disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 825 (0.12%)	1 / 827 (0.12%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	4 / 825 (0.48%)	7 / 827 (0.85%)	4 / 825 (0.48%)
occurrences causally related to treatment / all	0 / 4	0 / 9	1 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	4 / 825 (0.48%)	6 / 827 (0.73%)	2 / 825 (0.24%)
occurrences causally related to treatment / all	0 / 4	0 / 6	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Angina unstable			
subjects affected / exposed	2 / 825 (0.24%)	2 / 827 (0.24%)	2 / 825 (0.24%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	8 / 825 (0.97%)	5 / 827 (0.60%)	4 / 825 (0.48%)
occurrences causally related to treatment / all	0 / 9	0 / 10	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	1 / 825 (0.12%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
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 arrest			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	2 / 825 (0.24%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 825 (0.00%)	2 / 827 (0.24%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiac failure congestive			
subjects affected / exposed	1 / 825 (0.12%)	2 / 827 (0.24%)	2 / 825 (0.24%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			

subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory distress			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congestive cardiomyopathy			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Cor pulmonale			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Coronary artery disease			
subjects affected / exposed	5 / 825 (0.61%)	4 / 827 (0.48%)	7 / 825 (0.85%)
occurrences causally related to treatment / all	2 / 5	0 / 4	1 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery occlusion			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery stenosis			
subjects affected / exposed	2 / 825 (0.24%)	1 / 827 (0.12%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive heart disease			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Mitral valve incompetence			

subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	1 / 825 (0.12%)	3 / 827 (0.36%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	4 / 825 (0.48%)	0 / 827 (0.00%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	1 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Palpitations			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Pericarditis			
subjects affected / exposed	0 / 825 (0.00%)	2 / 827 (0.24%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis constrictive			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus tachycardia			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Supraventricular tachycardia			

subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (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
Tachycardia			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Ataxia			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Autonomic nervous system imbalance			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (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
Brain mass			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain stem haemorrhage			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carotid artery stenosis			
subjects affected / exposed	2 / 825 (0.24%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cauda equina syndrome			

subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral thrombosis			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrospinal fluid leakage			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Cerebrovascular accident			
subjects affected / exposed	1 / 825 (0.12%)	3 / 827 (0.36%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical radiculopathy			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	2 / 825 (0.24%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cognitive disorder			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dementia			

subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Depressed level of consciousness			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	2 / 825 (0.24%)	0 / 827 (0.00%)	2 / 825 (0.24%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysarthria			
subjects affected / exposed	1 / 825 (0.12%)	1 / 827 (0.12%)	0 / 825 (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
Encephalopathy			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Essential tremor			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	1 / 825 (0.12%)	1 / 827 (0.12%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	1 / 825 (0.12%)	1 / 827 (0.12%)	0 / 825 (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
Hemiparesis			

subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Hepatic encephalopathy			
subjects affected / exposed	1 / 825 (0.12%)	2 / 827 (0.24%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoaesthesia			
subjects affected / exposed	1 / 825 (0.12%)	2 / 827 (0.24%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial aneurysm			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial pressure increased			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Ischaemic stroke			
subjects affected / exposed	1 / 825 (0.12%)	3 / 827 (0.36%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lacunar stroke			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Lumbosacral radiculopathy			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic encephalopathy			

subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Migraine			
subjects affected / exposed	1 / 825 (0.12%)	4 / 827 (0.48%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Motor neurone disease			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Nerve compression			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorder			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Optic neuritis			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Parkinson's disease			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Parkinsonism			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Polyneuropathy			

subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post herpetic neuralgia			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	0 / 825 (0.00%)	3 / 827 (0.36%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 825 (0.00%)	2 / 827 (0.24%)	0 / 825 (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
Sensory disturbance			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal epidural haemorrhage			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			

subjects affected / exposed	7 / 825 (0.85%)	3 / 827 (0.36%)	5 / 825 (0.61%)
occurrences causally related to treatment / all	0 / 7	0 / 3	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thalamic infarction			
subjects affected / exposed	1 / 825 (0.12%)	1 / 827 (0.12%)	0 / 825 (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
Transient global amnesia			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Transient ischaemic attack			
subjects affected / exposed	1 / 825 (0.12%)	3 / 827 (0.36%)	3 / 825 (0.36%)
occurrences causally related to treatment / all	0 / 1	1 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Trigeminal neuralgia			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
VIIth nerve paralysis			
subjects affected / exposed	2 / 825 (0.24%)	1 / 827 (0.12%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 2	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VIth nerve paralysis			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertebrobasilar insufficiency			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	4 / 825 (0.48%)	2 / 827 (0.24%)	3 / 825 (0.36%)
occurrences causally related to treatment / all	0 / 4	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polycythaemia			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Splenic lesion			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Ear and labyrinth disorders			
Labyrinthine fistula			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertigo			
subjects affected / exposed	1 / 825 (0.12%)	2 / 827 (0.24%)	2 / 825 (0.24%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertigo positional			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			

Macular fibrosis			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Optic ischaemic neuropathy			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal detachment			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vision blurred			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	7 / 825 (0.85%)	4 / 827 (0.48%)	7 / 825 (0.85%)
occurrences causally related to treatment / all	1 / 7	0 / 9	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	2 / 825 (0.24%)	0 / 827 (0.00%)	2 / 825 (0.24%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal wall disorder			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal wall haematoma			

subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Apical granuloma			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendix disorder			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Ascites			
subjects affected / exposed	2 / 825 (0.24%)	2 / 827 (0.24%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ischaemic			
subjects affected / exposed	1 / 825 (0.12%)	1 / 827 (0.12%)	2 / 825 (0.24%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ulcerative			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colonic fistula			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Constipation			

subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	3 / 825 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 825 (0.00%)	4 / 827 (0.48%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum intestinal			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum intestinal haemorrhagic			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyschezia			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Dysphagia			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis			

subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric haemorrhage			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Gastric polyps			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer haemorrhage			
subjects affected / exposed	1 / 825 (0.12%)	2 / 827 (0.24%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis erosive			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	3 / 825 (0.36%)	3 / 827 (0.36%)	2 / 825 (0.24%)
occurrences causally related to treatment / all	0 / 3	0 / 3	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematochezia			

subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	2 / 825 (0.24%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impaired gastric emptying			
subjects affected / exposed	0 / 825 (0.00%)	3 / 827 (0.36%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 9	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incarcerated umbilical hernia			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Intestinal haemorrhage			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal ischaemia			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Intestinal obstruction			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	2 / 825 (0.24%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intra-abdominal haematoma			

subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Large intestine perforation			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Large intestine polyp			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melaena			
subjects affected / exposed	2 / 825 (0.24%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	2 / 825 (0.24%)	1 / 827 (0.12%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal obstruction			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Oesophageal varices haemorrhage			
subjects affected / exposed	0 / 825 (0.00%)	2 / 827 (0.24%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			

subjects affected / exposed	4 / 825 (0.48%)	6 / 827 (0.73%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	2 / 4	2 / 7	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	5 / 825 (0.61%)	1 / 827 (0.12%)	3 / 825 (0.36%)
occurrences causally related to treatment / all	2 / 6	1 / 1	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis haemorrhagic			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritoneal haemorrhage			
subjects affected / exposed	1 / 825 (0.12%)	1 / 827 (0.12%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Portal hypertensive gastropathy			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	2 / 825 (0.24%)	1 / 827 (0.12%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retroperitoneal haematoma			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	2 / 825 (0.24%)	5 / 827 (0.60%)	5 / 825 (0.61%)
occurrences causally related to treatment / all	0 / 2	0 / 6	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			

subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical hernia			
subjects affected / exposed	1 / 825 (0.12%)	1 / 827 (0.12%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varices oesophageal			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Vomiting			
subjects affected / exposed	2 / 825 (0.24%)	2 / 827 (0.24%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 825 (0.00%)	2 / 827 (0.24%)	0 / 825 (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
Decubitus ulcer			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dermatomyositis			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic foot			

subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hidradenitis			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lichen sclerosus			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Pruritus			
subjects affected / exposed	0 / 825 (0.00%)	5 / 827 (0.60%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	5 / 5	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin ulcer			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	6 / 825 (0.73%)	13 / 827 (1.57%)	4 / 825 (0.48%)
occurrences causally related to treatment / all	0 / 6	3 / 14	0 / 4
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Bladder prolapse			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Calculus ureteric			
subjects affected / exposed	2 / 825 (0.24%)	1 / 827 (0.12%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Calculus urinary			

subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis haemorrhagic			
subjects affected / exposed	0 / 825 (0.00%)	2 / 827 (0.24%)	0 / 825 (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
Diabetic nephropathy			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower urinary tract symptoms			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	5 / 825 (0.61%)	5 / 827 (0.60%)	5 / 825 (0.61%)
occurrences causally related to treatment / all	0 / 6	0 / 8	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvi-ureteric obstruction			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal aneurysm			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal colic			

subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
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 failure			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureteric obstruction			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urethral stenosis			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Endocrine disorders			
Adrenal haematoma			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Goitre			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Pituitary-dependent Cushing's syndrome			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroid mass			

subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroiditis subacute			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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			
Arthralgia			
subjects affected / exposed	1 / 825 (0.12%)	1 / 827 (0.12%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis			
subjects affected / exposed	3 / 825 (0.36%)	2 / 827 (0.24%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	1 / 825 (0.12%)	1 / 827 (0.12%)	2 / 825 (0.24%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone disorder			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
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 spinal stenosis			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Costochondritis			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture nonunion			

subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Gouty arthritis			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inclusion body myositis			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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 degeneration			
subjects affected / exposed	2 / 825 (0.24%)	0 / 827 (0.00%)	2 / 825 (0.24%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	3 / 825 (0.36%)	3 / 827 (0.36%)	6 / 825 (0.73%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar spinal stenosis			
subjects affected / exposed	1 / 825 (0.12%)	1 / 827 (0.12%)	2 / 825 (0.24%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	1 / 825 (0.12%)	3 / 827 (0.36%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myalgia			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	2 / 825 (0.24%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myopathy			

subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myositis			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Osteoarthritis			
subjects affected / exposed	6 / 825 (0.73%)	8 / 827 (0.97%)	6 / 825 (0.73%)
occurrences causally related to treatment / all	0 / 8	0 / 9	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis of jaw			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Polymyalgia rheumatica			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psoriatic arthropathy			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhabdomyolysis			
subjects affected / exposed	0 / 825 (0.00%)	2 / 827 (0.24%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotator cuff syndrome			

subjects affected / exposed	1 / 825 (0.12%)	1 / 827 (0.12%)	0 / 825 (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
Spinal column stenosis			
subjects affected / exposed	3 / 825 (0.36%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal osteoarthritis			
subjects affected / exposed	2 / 825 (0.24%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spondylolisthesis			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon calcification			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertebral foraminal stenosis			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	2 / 825 (0.24%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess limb			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal infection			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis perforated			

subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis bacterial			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Bronchiolitis			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	3 / 825 (0.36%)	5 / 827 (0.60%)	6 / 825 (0.73%)
occurrences causally related to treatment / all	0 / 3	0 / 5	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis infective			
subjects affected / exposed	1 / 825 (0.12%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic sinusitis			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Clostridium difficile colitis			
subjects affected / exposed	0 / 825 (0.00%)	3 / 827 (0.36%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile infection			

subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coccidioidomycosis			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Corona virus infection			
subjects affected / exposed	6 / 825 (0.73%)	7 / 827 (0.85%)	6 / 825 (0.73%)
occurrences causally related to treatment / all	0 / 6	0 / 7	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	0 / 825 (0.00%)	3 / 827 (0.36%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cytomegalovirus mononucleosis			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (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
Diarrhoea infectious			
subjects affected / exposed	2 / 825 (0.24%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	3 / 825 (0.36%)	2 / 827 (0.24%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	1 / 3	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalitis viral			

subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Endocarditis bacterial			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Escherichia sepsis			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gangrene			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	2 / 825 (0.24%)	4 / 827 (0.48%)	2 / 825 (0.24%)
occurrences causally related to treatment / all	0 / 2	0 / 5	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Graft infection			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Groin abscess			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Helicobacter infection			

subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis E			
subjects affected / exposed	1 / 825 (0.12%)	1 / 827 (0.12%)	0 / 825 (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
Histoplasmosis			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Infection			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Influenza			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint abscess			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Kidney infection			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver abscess			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Localised infection			

subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mastoiditis			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Medical device site joint infection			
subjects affected / exposed	1 / 825 (0.12%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Parotid abscess			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic abscess			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Perirectal abscess			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	1 / 825 (0.12%)	1 / 827 (0.12%)	0 / 825 (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
Pharyngeal abscess			

subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Pneumonia			
subjects affected / exposed	5 / 825 (0.61%)	9 / 827 (1.09%)	7 / 825 (0.85%)
occurrences causally related to treatment / all	0 / 5	0 / 9	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia viral			
subjects affected / exposed	9 / 825 (1.09%)	10 / 827 (1.21%)	4 / 825 (0.48%)
occurrences causally related to treatment / all	0 / 9	0 / 10	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural cellulitis			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural infection			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural sepsis			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Postoperative wound infection			
subjects affected / exposed	2 / 825 (0.24%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudomonas infection			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary sepsis			

subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Pyelonephritis			
subjects affected / exposed	5 / 825 (0.61%)	4 / 827 (0.48%)	3 / 825 (0.36%)
occurrences causally related to treatment / all	0 / 6	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotavirus infection			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salmonellosis			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	7 / 825 (0.85%)	6 / 827 (0.73%)	7 / 825 (0.85%)
occurrences causally related to treatment / all	0 / 8	0 / 6	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis syndrome			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Septic encephalopathy			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 825 (0.00%)	3 / 827 (0.36%)	3 / 825 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			

subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Staphylococcal infection			
subjects affected / exposed	1 / 825 (0.12%)	2 / 827 (0.24%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal bacteraemia			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Streptococcal sepsis			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous abscess			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Tonsillitis			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth infection			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Tracheobronchitis			

subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
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 respiratory tract infection			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Urinary tract infection			
subjects affected / exposed	3 / 825 (0.36%)	5 / 827 (0.60%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	2 / 825 (0.24%)	3 / 827 (0.36%)	2 / 825 (0.24%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicella			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vestibular neuronitis			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Viral pericarditis			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vulval abscess			
subjects affected / exposed	1 / 825 (0.12%)	1 / 827 (0.12%)	0 / 825 (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
Wound infection			

subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 825 (0.12%)	1 / 827 (0.12%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus			
subjects affected / exposed	0 / 825 (0.00%)	4 / 827 (0.48%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus inadequate control			
subjects affected / exposed	3 / 825 (0.36%)	3 / 827 (0.36%)	2 / 825 (0.24%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	3 / 825 (0.36%)	2 / 827 (0.24%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 4	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrolyte imbalance			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Failure to thrive			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fluid overload			
subjects affected / exposed	0 / 825 (0.00%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gout			

subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Hypercreatininaemia			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Hyperglycaemia			
subjects affected / exposed	0 / 825 (0.00%)	2 / 827 (0.24%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	0 / 825 (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
Hypoglycaemia			
subjects affected / exposed	1 / 825 (0.12%)	1 / 827 (0.12%)	2 / 825 (0.24%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	2 / 825 (0.24%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lactic acidosis			
subjects affected / exposed	0 / 825 (0.00%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obesity			

subjects affected / exposed	1 / 825 (0.12%)	0 / 827 (0.00%)	1 / 825 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 825 (0.12%)	1 / 827 (0.12%)	0 / 825 (0.00%)
occurrences causally related to treatment / all	0 / 1	2 / 2	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	OCA 10 Milligrams (mg)	OCA 25 mg	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	801 / 825 (97.09%)	814 / 827 (98.43%)	782 / 825 (94.79%)
Vascular disorders			
Hypertension			
subjects affected / exposed	106 / 825 (12.85%)	97 / 827 (11.73%)	88 / 825 (10.67%)
occurrences (all)	114	102	94
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	148 / 825 (17.94%)	135 / 827 (16.32%)	138 / 825 (16.73%)
occurrences (all)	176	159	158
Oedema peripheral			
subjects affected / exposed	47 / 825 (5.70%)	39 / 827 (4.72%)	42 / 825 (5.09%)
occurrences (all)	53	47	48
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	81 / 825 (9.82%)	69 / 827 (8.34%)	62 / 825 (7.52%)
occurrences (all)	96	84	72
Psychiatric disorders			
Depression			
subjects affected / exposed	63 / 825 (7.64%)	54 / 827 (6.53%)	62 / 825 (7.52%)
occurrences (all)	71	60	64
Anxiety			
subjects affected / exposed	45 / 825 (5.45%)	54 / 827 (6.53%)	42 / 825 (5.09%)
occurrences (all)	48	57	45

Insomnia			
subjects affected / exposed	68 / 825 (8.24%)	55 / 827 (6.65%)	48 / 825 (5.82%)
occurrences (all)	71	60	48
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	37 / 825 (4.48%)	26 / 827 (3.14%)	49 / 825 (5.94%)
occurrences (all)	42	31	62
Aspartate aminotransferase increased			
subjects affected / exposed	38 / 825 (4.61%)	27 / 827 (3.26%)	46 / 825 (5.58%)
occurrences (all)	40	33	54
Blood cholesterol increased			
subjects affected / exposed	53 / 825 (6.42%)	51 / 827 (6.17%)	32 / 825 (3.88%)
occurrences (all)	60	55	33
Blood creatinine increased			
subjects affected / exposed	53 / 825 (6.42%)	43 / 827 (5.20%)	43 / 825 (5.21%)
occurrences (all)	83	60	58
Gamma-glutamyltransferase increased			
subjects affected / exposed	28 / 825 (3.39%)	14 / 827 (1.69%)	43 / 825 (5.21%)
occurrences (all)	37	18	49
Glycosylated haemoglobin increased			
subjects affected / exposed	47 / 825 (5.70%)	40 / 827 (4.84%)	37 / 825 (4.48%)
occurrences (all)	50	48	43
Low density lipoprotein increased			
subjects affected / exposed	175 / 825 (21.21%)	183 / 827 (22.13%)	92 / 825 (11.15%)
occurrences (all)	201	207	107
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	45 / 825 (5.45%)	33 / 827 (3.99%)	44 / 825 (5.33%)
occurrences (all)	57	37	55
Procedural pain			
subjects affected / exposed	58 / 825 (7.03%)	50 / 827 (6.05%)	44 / 825 (5.33%)
occurrences (all)	64	58	58
Nervous system disorders			
Dizziness			

subjects affected / exposed	62 / 825 (7.52%)	53 / 827 (6.41%)	55 / 825 (6.67%)
occurrences (all)	67	59	71
Headache			
subjects affected / exposed	83 / 825 (10.06%)	87 / 827 (10.52%)	90 / 825 (10.91%)
occurrences (all)	108	97	116
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	59 / 825 (7.15%)	57 / 827 (6.89%)	48 / 825 (5.82%)
occurrences (all)	66	66	51
Abdominal pain			
subjects affected / exposed	139 / 825 (16.85%)	135 / 827 (16.32%)	132 / 825 (16.00%)
occurrences (all)	178	173	172
Abdominal pain upper			
subjects affected / exposed	95 / 825 (11.52%)	104 / 827 (12.58%)	106 / 825 (12.85%)
occurrences (all)	112	135	129
Constipation			
subjects affected / exposed	115 / 825 (13.94%)	128 / 827 (15.48%)	92 / 825 (11.15%)
occurrences (all)	128	146	99
Diarrhoea			
subjects affected / exposed	112 / 825 (13.58%)	108 / 827 (13.06%)	145 / 825 (17.58%)
occurrences (all)	145	146	205
Dyspepsia			
subjects affected / exposed	48 / 825 (5.82%)	35 / 827 (4.23%)	41 / 825 (4.97%)
occurrences (all)	58	38	52
Gastrooesophageal reflux disease			
subjects affected / exposed	51 / 825 (6.18%)	63 / 827 (7.62%)	47 / 825 (5.70%)
occurrences (all)	55	70	51
Nausea			
subjects affected / exposed	148 / 825 (17.94%)	165 / 827 (19.95%)	150 / 825 (18.18%)
occurrences (all)	211	211	187
Vomiting			
subjects affected / exposed	71 / 825 (8.61%)	90 / 827 (10.88%)	66 / 825 (8.00%)
occurrences (all)	92	115	81
Hepatobiliary disorders			
Cholelithiasis			

subjects affected / exposed	50 / 825 (6.06%)	66 / 827 (7.98%)	30 / 825 (3.64%)
occurrences (all)	55	72	36
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	294 / 825 (35.64%)	470 / 827 (56.83%)	210 / 825 (25.45%)
occurrences (all)	429	907	286
Pruritus generalised			
subjects affected / exposed	15 / 825 (1.82%)	55 / 827 (6.65%)	13 / 825 (1.58%)
occurrences (all)	16	79	14
Rash			
subjects affected / exposed	46 / 825 (5.58%)	61 / 827 (7.38%)	48 / 825 (5.82%)
occurrences (all)	59	68	59
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	117 / 825 (14.18%)	132 / 827 (15.96%)	134 / 825 (16.24%)
occurrences (all)	143	154	161
Back pain			
subjects affected / exposed	136 / 825 (16.48%)	105 / 827 (12.70%)	120 / 825 (14.55%)
occurrences (all)	159	121	155
Muscle spasms			
subjects affected / exposed	47 / 825 (5.70%)	49 / 827 (5.93%)	60 / 825 (7.27%)
occurrences (all)	53	58	73
Musculoskeletal pain			
subjects affected / exposed	65 / 825 (7.88%)	53 / 827 (6.41%)	61 / 825 (7.39%)
occurrences (all)	78	64	65
Pain in extremity			
subjects affected / exposed	67 / 825 (8.12%)	67 / 827 (8.10%)	66 / 825 (8.00%)
occurrences (all)	76	78	75
Infections and infestations			
Bronchitis			
subjects affected / exposed	81 / 825 (9.82%)	66 / 827 (7.98%)	66 / 825 (8.00%)
occurrences (all)	107	80	83
Influenza			
subjects affected / exposed	61 / 825 (7.39%)	63 / 827 (7.62%)	59 / 825 (7.15%)
occurrences (all)	66	69	66
Nasopharyngitis			

subjects affected / exposed	82 / 825 (9.94%)	80 / 827 (9.67%)	70 / 825 (8.48%)
occurrences (all)	113	105	103
Sinusitis			
subjects affected / exposed	74 / 825 (8.97%)	73 / 827 (8.83%)	80 / 825 (9.70%)
occurrences (all)	93	113	130
Upper respiratory tract infection			
subjects affected / exposed	88 / 825 (10.67%)	103 / 827 (12.45%)	84 / 825 (10.18%)
occurrences (all)	117	131	108
Urinary tract infection			
subjects affected / exposed	147 / 825 (17.82%)	151 / 827 (18.26%)	133 / 825 (16.12%)
occurrences (all)	229	239	210
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	112 / 825 (13.58%)	99 / 827 (11.97%)	94 / 825 (11.39%)
occurrences (all)	134	120	111
Hypercholesterolaemia			
subjects affected / exposed	57 / 825 (6.91%)	48 / 827 (5.80%)	26 / 825 (3.15%)
occurrences (all)	60	51	30
Hyperlipidaemia			
subjects affected / exposed	80 / 825 (9.70%)	90 / 827 (10.88%)	33 / 825 (4.00%)
occurrences (all)	84	97	33
Type 2 diabetes mellitus			
subjects affected / exposed	70 / 825 (8.48%)	47 / 827 (5.68%)	60 / 825 (7.27%)
occurrences (all)	72	50	61

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 September 2015	Amended to incorporate feedback received from regulatory authorities (RA) and to clarify various aspects of the study design. Protocol V2 was published internally at ICPT but was not submitted to any RAs, Ethics Committees (ECs) or sites. Instead Protocol V3 dated 30Sep2015 was released to RAs, ECs and sites. Changes to the assessments, such as more frequent hepatocellular carcinoma screenings, were implemented to expedite identification of potential liver-related clinical outcomes. In addition, minor formatting and editorial changes were done (not listed in the summary of changes table).
30 September 2015	Amended to add definitions from Chapters 8 through 10 of "Standardized Definitions for Cardiovascular and Stroke Endpoint Events in Clinical Trials," dated August 20, 2014 to Appendix D. Additionally, the protocol was edited to clarify that subjects will be required to participate in noninvasive radiological liver fibrosis measurements at selected centers where the devices are available.
17 December 2015	Sweden: Amended to add clarifying information showing that OCA may increase the exposure of narrow therapeutic index drugs that are substrates for CYP1A2, to answer questions raised by regulatory authorities
21 December 2015	France: Amended to exclude subjects with acute cholecystitis or a biliary obstruction and to clarify that bile acid sequestrants include colestyramine and its derivatives colestipol, colesevelam or other sequestrants.
08 April 2016	Switzerland Addendum 1: Created to clarify the contraception use as designated inclusion criteria 6 at the request of the Swiss ECs. (Format of this was a memo to Investigators and other relevant parties in Switzerland, signed by CH general manager as the sponsor representative and by PIs in CH as agree to conduct as per this addendum)
14 April 2016	Amended to add: - Chronic Liver Disease Questionnaire - NAFLD and the Work Productivity and Activity Index to further assess health-related quality of life - Multi-parametric magnetic resonance imaging to the list of non-invasive radiological measurements of liver fibrosis. - Expanded the list of conjugates or metabolites of OCA for assessment to include OCA glucuronide. - A list of events that are disease-related and exempt from expeditious regulatory reporting was added so that unblinding of a SUSAR that is also a clinical outcomes event would not disqualify the event from adjudication. - The requirement for subjects to not take or be on a stable dose of drugs with potential NASH-modifying properties for 6 months before Day 1 was limited to subjects providing historical biopsies to determine study eligibility. - Specific restrictions for diabetes and weight loss pharmacotherapies were removed as was the requirement for allowed concomitant medications and supplements to be stable for 30 days before Day 1. - Additionally, various aspects of study design and study population were clarified - Feedback from Swedish & French regulatory agencies was incorporated. (Protocol v3.1 & 3.2)
18 May 2016	EU Countries: Section 2 (Synopsis) was revised to add the full list of bullets for exclusion criteria 4 that are listed in section 8.1.2 (subject exclusion criteria)

14 November 2016	Amended to change the number of central pathologists needed to determine histological presence of NASH for study eligibility from 2 to 1 Rationale: For Version 4 of the protocol, the histology evaluation procedure at Screening for eligibility required that slides from subjects deemed eligible for participation by the initial pathologist to be sent to a second pathologist for confirmation of eligibility. Given that the second confirmatory reading was generally concordant with the first for the subjects evaluated thus far, only 1 pathologist will now be required to determine study eligibility. - Add option for subjects who successfully complete the EOT/EOS Visit upon closing of the Study 747-303 to receive open-label OCA for up to 5 years in an extension study. - Additionally, various aspects of the study design and study population were clarified.
30 March 2017	Denmark Addendum 1: Removes all reference made to the 5-year open label extension study
19 September 2017	Safety Amendment: Protocol version 5.0 was amended to address the evolution of the clinical research of NASH and discussions with the US FDA. This appendix summarizes changes made to the protocol per Safety Amendment dated 19 Sep 2017. Additional changes clarifying the objectives, interim and final analyses, and modifications of assessments and procedures are summarized in Appendix J. The Safety Amendment dated was prepared in consultation with the FDA to develop procedures to closely monitor subjects and ensure early identification of potential decompensation and/or liver injury. The amendment proposed more extensive safety monitoring procedures and appropriate dosing adjustments, interruptions, and discontinuations to improve subject oversight and safety including: • Educating the Investigators and subjects about the signs and symptoms of potential hepatic injury and progression to cirrhosis and/or decompensation and the importance of appropriate follow-up and dose adjustments. Key components of safety monitoring and dose adjustment procedures include: - Telephone contact every 2 weeks to: - Review the signs and symptoms of potential hepatic injury and decompensation - Determine if the subject had any recent interaction with other health care professionals (HCPs) - Laboratory assessments every 6 weeks to review specific biochemical triggers and clinical criteria for monitoring potential hepatic injury or decompensation - Criteria for interruption or discontinuation of investigational product, as well as rules for possible re-challenge and dose adjustments in the event of: - Hepatic injury - Progression to cirrhosis and/or decompensation Criteria for close observation of subjects with suspected hepatic injury or progression to cirrhosis or decompensation

02 October 2017	The Introduction was revised to highlight the need for close monitoring specifically in patients with clinical evidence of hepatic decompensation and other complications due to progression of disease. The primary objective assessed at Month 18 was revised to replace the analysis of the coprimary endpoints with the analysis of multiple primary endpoints. Definition of NASH resolution clarified. Exploratory objective assessed at Month 18 was revised to include morphometric assessment of histology sections for only collagen and not fat. The study design was modified to increase enrolment to approximately 2085 subjects with biopsy-confirmed stage 2 or stage 3 liver fibrosis. An additional cohort of approximately 285 subjects with stage 1 fibrosis with at least 1 accompanying comorbidity will be enrolled to gather information on the safety of OCA and progression of liver disease in this population. The study design was also modified to increase accrual from 1 year to a 2year period. The study design and determination of sample size sections describe changes in the interim analysis sample size to reflect the revised powering assumptions for the interim analysis of primary endpoints and the increased accrual period. A description of procedures to assess progression of liver disease was added. Guidance for management of disease progression was added including procedures for dose adjustment for subjects who have disease progression and procedures for interruption and discontinuation of investigational product for safety were added. Procedures were added for collecting blood samples to determine the PK of OCA and its metabolites in subjects with disease progression. Guidance was added that subjects and investigators should be instructed to contact the site and Medical Monitor, respectively upon awareness of development in signs and symptoms of potential hepatic decompensation. Guidance added to monitor amylase and lipase levels in subjects with suspected acute pancreatitis.
17 November 2017	Switzerland Addendum 2: Country specific protocol addendum to clarify the contraception use as designated in Inclusion criteria 6 and associated text in the protocol for subjects enrolled at sites in Switzerland. Updated to be consistent with the contraception expectations required by CH regulatory authorities.
02 January 2018	Addendum 1 Country Specific US: Amended to incorporate Month 2 visit for subjects enrolled at sites in USA to comply with FDA request to perform monthly physical exams and labs for the 1st 3 months
11 April 2018	Information added to clarify secondary and exploratory objectives, revised secondary objectives order. Clarified changes in fibrosis and included effects on liver biochemistry and measures of liver function as secondary analysis to support efficacy. Safety amendment assessments of telephone contacts every 2 weeks and laboratory visits every 6 weeks were removed. New information added on summary of known potential risks of OCA. Information added to clarify monitoring and assessment of subjects who may be at risk for suspected hepatic injury or decompensation, by providing specific guidance to investigators to educate subjects, monitor subjects for signs and symptoms of suspected hepatic injury or decompensation as well as criteria for study drug interruption or discontinuation. Instructions included to discontinue IP and obtain a liver biopsy in subjects who undergo bariatric surgery during study. Guidance added to inform Investigator to notify the Medical Monitor when deciding to discontinue IP. The windows for Month 18 and Month 48 visits are expanded. The –6-week limit is more reflective of way data points are assigned to visits for analyses, but upper limit was kept at +2 to expedite data collection and lock. Month 48 visit window expanded (8 weeks) to +/- 4 weeks to allow scheduling of biopsies. Exploratory assessments reduced or streamlined to reduce subject burden including: Stopping collection of blood samples for future analyses and genetic analyses. Limit assessments of noninvasive serum and radiological assessments of fibrosis to a subset of subjects. Assessment of stool samples for microbiome is being limited to those subjects who provided baseline samples only and will not be collected from newly enrolled. Revisions provided to clarify statistical analyses of primary, secondary, and exploratory endpoints. Appendix B revised to provide guidance to Investigators to educate subjects and evaluate signs and symptoms of hepatic injury and decompensation.
01 May 2018	US Addendum 1 Admin Letter: Updated the contact info for the medical monitor. Addendum 1 Clarification letter: Clarification of addendum 1: 2Jan2018 for US – that a Physical Examination will be performed for new subjects at Months 1, 2 & 3.

08 January 2019	Protocol 747-303 has been updated to version 8 to include the following key changes: - Information was added for the implementation of the new requirements for IP interruption and medical management procedures for subjects with symptomatic cholelithiasis and/or cholecystitis. - A number of updates were made to the statistical section of the protocol based on interactions with Health Authorities. - Hepatocellular carcinoma (HCC) was removed from primary composite endpoint based on recommendations from Health Authorities.
09 July 2019	Amended to include the following information: 1) Month 18 biopsy removed 2) ARFI removed as an assessment 3) 10-year ASCVD Risk added as an assessment 4) Additional strategies and procedures for subject retention
02 October 2019	Admin Letter to Prot V9.0: To explain the error in the synopsis regarding the diagram of the study timeline.
03 February 2020	Amended to include the following information: 1) DMC recommendation for treatment-emergent acute or nonacute pancreatitis 2) Liver biopsy for suspected progression to cirrhosis 3) Highly effective contraception language per CTFG guidance 4) SUSAR definition per ICH guidance
01 May 2020	The restrictions that have recently been imposed to contain the global COVID-19 pandemic, such as social distancing measures, stay at home orders, and other limitations have impeded the ability of subjects and site staff to complete protocol-specified procedures. Some study sites are not able to perform protocol-specified procedures and assessments. In addition, some subjects are unable to return to study sites for evaluations and/or to receive continued supply of investigational product (IP). The purpose of this Country-Specific Protocol Addendum is to describe the requirements and processes under which subjects who are unable to return to study sites may complete protocol specified assessments and continue to receive investigational product until in-person site visits can resume. In an effort to minimize the potential adverse impact of restrictions from the COVID-19 pandemic on achieving the objectives of the study, while continuing to ensure the safety of participating subjects, the following approaches will apply to the study protocol, effective immediately.

04 May 2021	1) Update to the end-of-study primary objective for progression of cirrhosis to include all clinical evidence beyond only histological changes 2) Inclusion of Hepatic Safety Adjudication Committee and Renal Adjudication Committee for the adjudication of all events of potential hepatic injury and acute kidney injury, respectively. The protocol was updated to ensure these events will be provided to the DMC for inclusion in their review as well as added to the Safety Objectives to be assessed at the End of Study. 3) Updated process for the monitoring and management of potential DILI and updated the DILI algorithm and laboratory triggers to monitor hepatic injury 4) Clarification of language on PK sample collection following investigational product interruption or discontinuation due to suspected hepatic injury and progression to cirrhosis, within 7 days of experiencing a serious adverse event, and at the time of liver biopsy. Additional PK sparse sample collection was added to each study visit after Month 18 to adequately capture the OCA exposure-response relationships for efficacy and safety 5) Additional sections added to address monitoring and management of renal impairment and nephrolithiasis, hyperglycemia, and dyslipidemia. Additional education and assessments to identify intercurrent illness and/or potential adverse events was added to each study visit after Month 18. 6) Inclusion of local laboratory results and reference ranges into the eCRF and inclusion local pathology reports into the eCRF 7) COVID-19 related changes to the protocol 8) The use of "suspected" was globally updated to "potential" throughout the protocol 9) Study duration was updated from 7 to 10 years based on current estimates for outcome accrual 10) Previous Summary of Changes for each protocol amendment removed. Moving forward, only the current Summary of Changes will be included.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
15 November 2023	On 22 Jun 2023, Intercept received a Complete Response Letter (CRL) from the FDA stating that the new drug application (NDA) could not be approved in its present form. Based on the content of the CRL, any resubmission of an NDA for OCA in NASH would require, at a minimum, successful completion of the long-term outcomes phase of the REGENERATE study. The 747-303 study was terminated with only critical data fields cleaned which consisted of all deaths, hepatic serious adverse events (SAEs), all adjudicated Month 48 biopsies collected through 30 Jun 2023, end of treatment/end of study (EOS) status for all subjects, and medication exposure.	-

Notes:

Limitations and caveats

None reported