



Clinical trial results:

A Randomised, Double-blind, Multicentre Phase II/III Study to Compare the Efficacy of AZD2171 in Combination with 5-fluorouracil, Leucovorin, and Oxaliplatin (FOLFOX), to the Efficacy of Bevacizumab in Combination with FOLFOX in Patients with Previously Untreated Metastatic Colorectal Cancer

Summary

EudraCT number	2005-003440-66
Trial protocol	BE AT CZ DE SK HU IT GB FI LV MT
Global end of trial date	19 August 2015

Results information

Result version number	v1 (current)
This version publication date	08 November 2017
First version publication date	08 November 2017

Trial information

Trial identification

Sponsor protocol code	D8480C00013
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	132 Hills Road, Cambridge, United Kingdom, CB2 1PG
Public contact	Tsveta Milenkova, AstraZeneca, ClinicalTrialTransparency@astrazeneca.com
Scientific contact	Tsveta Milenkova, AstraZeneca, ClinicalTrialTransparency@astrazeneca.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	01 October 2010
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 November 2009
Global end of trial reached?	Yes
Global end of trial date	19 August 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is a phase II/III study to compare the efficacy of AZD2171 in combination with FOLFOX to the efficacy of FOLFOX in combination with bevacizumab

Protection of trial subjects:

On completion of the phase II part of the study and following review by an Independent Data Monitoring Committee (IDMC), if there is a clear difference between the two doses then the patients from the discontinued dose will be unblinded and given the option to continue treatment on their current dose of AZD2171 or to switch to the dose of AZD2171 selected for the phase III study.

If toxicity is encountered, the dose of AZD2171 may be reduced or treatment with AZD2171 and bevacizumab stopped until resolution of symptoms. At the discretion of the investigator, treatment may then be restarted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 August 2006
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	Australia: 243
Country: Number of subjects enrolled	Austria: 53
Country: Number of subjects enrolled	Belgium: 156
Country: Number of subjects enrolled	Canada: 68
Country: Number of subjects enrolled	Czech Republic: 120
Country: Number of subjects enrolled	Egypt: 28
Country: Number of subjects enrolled	Finland: 5
Country: Number of subjects enrolled	France: 35
Country: Number of subjects enrolled	Germany: 58
Country: Number of subjects enrolled	Hungary: 162
Country: Number of subjects enrolled	India: 39
Country: Number of subjects enrolled	Israel: 28
Country: Number of subjects enrolled	Italy: 78
Country: Number of subjects enrolled	Latvia: 7
Country: Number of subjects enrolled	Malta: 20
Country: Number of subjects enrolled	Philippines: 28
Country: Number of subjects enrolled	Poland: 51

Country: Number of subjects enrolled	Russian Federation: 25
Country: Number of subjects enrolled	Slovakia: 21
Country: Number of subjects enrolled	South Africa: 23
Country: Number of subjects enrolled	Spain: 99
Country: Number of subjects enrolled	Taiwan: 9
Country: Number of subjects enrolled	Thailand: 15
Country: Number of subjects enrolled	Turkey: 11
Country: Number of subjects enrolled	United Kingdom: 109
Country: Number of subjects enrolled	Ukraine: 270
Country: Number of subjects enrolled	United States: 25
Country: Number of subjects enrolled	Vietnam: 19
Worldwide total number of subjects	1805
EEA total number of subjects	974

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)	1213
From 65 to 84 years	590
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Phase II patients: 74 (Cediranib 20mg), 76 (Cediranib 30mg), 76 (Bevacizumab 5 mg/kg)

Full Analysis Set (ITT) : 709 (Cediranib 20mg), 713 (Bevacizumab 5 mg/kg)

Per Protocol Set : 702 (Cediranib 20mg), 696 (Bevacizumab 5 mg/kg)

Safety Set (ITT) : 705 (Cediranib 20mg), 704 (Bevacizumab 5 mg/kg)

Pre-assignment

Screening details:

Cediranib 30 mg discontinued following Phase II, Cediranib 20 mg chosen dose for comparing with Bevacizumab. 1805 patients enrolled to the study, 1614 patients were randomised, and 1600 received randomised treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cediranib 20 mg

Arm description:

Cediranib 20 mg/day + FOLFOX + bevacizumab placebo

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

Dosage and administration details:

20 mg orally once daily

Arm title	Bevacizumab 5 mg/kg
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Arm description:

Bevacizumab + FOLFOX + cediranib placebo

Arm type	Active comparator
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

5mg/kg every 14 days

Number of subjects in period 1^[1]	Cediranib 20 mg	Bevacizumab 5 mg/kg
Started	709	713
Completed	397	394
Not completed	312	319
Consent withdrawn by subject	52	48
Other	3	3
Death	239	247
Incorrect enrolment/eligib not fulfilled	2	3
Lost to follow-up	16	18

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The study was a phase 2/3 study and had three arms. Two arms were continued from the phase 2 period into the phase 3 period, and the 30mg arm was dropped. The final analysis was based on the entirety of the data collected for the two arms, therefore due to the structure of pharmaCM we had to enter these two arms into an "overall study" period, and then entered the 30mg arm into a separate study period named "Phase II period (Cediranib 30mg only)".

Period 2

Period 2 title	Phase II period (Cediranib 30mg only)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Arm title	Cediranib 30 mg
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Cediranib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

30 mg orally once daily

Number of subjects in period 2^[2]	Cediranib 30 mg
Started	192
Completed	7
Not completed	185
Adverse event, non-fatal	55
Other	12

Condition under investigation worsened	84
Voluntary discontinuation by patient	34

Notes:

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

Justification: The number of patients enrolled to a trial isn't always equal to the number randomised due to things like screening failures. Therefore the numbers randomised to treatment on study in this case are less than the number enrolled.

Baseline characteristics

Reporting groups

Reporting group title	Cediranib 20 mg
Reporting group description: Cediranib 20 mg/day + FOLFOX + bevacizumab placebo	
Reporting group title	Bevacizumab 5 mg/kg
Reporting group description: Bevacizumab + FOLFOX + cediranib placebo	

Reporting group values	Cediranib 20 mg	Bevacizumab 5 mg/kg	Total
Number of subjects	709	713	1422
Age Categorical Units: Subjects			
≥18 to <65 years	501	461	962
≥65 to <75 years	166	209	375
≥75 years	42	43	85
Age Continuous Units: years			
arithmetic mean	58.1	59	
standard deviation	± 11.37	± 10.82	-
Gender Categorical Units: Subjects			
Female	297	299	596
Male	412	414	826
Race Units: Subjects			
Caucasian	679	666	1345
Oriental	24	40	64
Black	4	4	8
Other	2	3	5
Ethnic group Units: Subjects			
Not applicable	659	646	1305
Asian	37	53	90
Chinese	6	5	11
African	4	1	5
African-American	1	3	4
Hispanic	1	2	3
Other	1	3	4
BMI Units: Kg/m2			
arithmetic mean	25.56	25.81	
standard deviation	± 4.57	± 5.15	-

End points

End points reporting groups

Reporting group title	Cediranib 20 mg
Reporting group description: Cediranib 20 mg/day + FOLFOX + bevacizumab placebo	
Reporting group title	Bevacizumab 5 mg/kg
Reporting group description: Bevacizumab + FOLFOX + cediranib placebo	
Reporting group title	Cediranib 30 mg
Reporting group description: -	

Primary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)
End point description: The efficacy of cediranib in combination with FOLFOX compared to the efficacy of bevacizumab in combination with FOLFOX by assessment of PFS. For PFS only, non-inferiority, in addition to superiority, of cediranib compared to bevacizumab will also be assessed, as outlined below: <ul style="list-style-type: none">• if the hazard ratio is < 1 and the p-value is < 0.05, we will conclude that cediranib provides a statistically significant improvement in PFS compared to bevacizumab alone.• if the upper 2-sided 95% confidence limit for the hazard ratio is < 1.2, we will conclude non-inferiority of cediranib compared to bevacizumab with respect to PFS• if the non-inferiority criteria is not reached, and the p-value is > 0.05, we will conclude that there is no statistically significant difference between the treatment groups.• if the hazard ratio is > 1, the p-value is < 0.05, we will conclude the cediranib is inferior to bevacizumab.	
End point type	Primary
End point timeframe: RECIST assessed at baseline, then at 8 weekly intervals for 24 weeks, and then every 12 weeks thereafter through to progression or data cut off date of 15/11/09 whichever was earliest.	

End point values	Cediranib 20 mg	Bevacizumab 5 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	709	713		
Units: Months				
median (inter-quartile range (Q1-Q3))				
Median PFS	9.9 (6.3 to 13.5)	10.3 (6.5 to 14.1)		

Statistical analyses

Statistical analysis title	Primary Analysis
Statistical analysis description: PFS will be analysed using a log-rank test stratified by performance status (PS, 0 or 1), baseline albumin	

and baseline ALP, the variables used in the stratified randomisation scheme for the study. Any patient in the study with a baseline performance status of 2 or greater (an important protocol deviation) will be included in the PS 1 category in all formal statistical analysis

Comparison groups	Cediranib 20 mg v Bevacizumab 5 mg/kg
Number of subjects included in analysis	1422
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.119
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.97
upper limit	1.25

Statistical analysis title	Sensitivity (Alternative censoring mechanism)
Statistical analysis description:	
All progression or death events are included in the analysis, regardless of whether they follow missing, or incomplete RECIST assessments, or if they occur after a patient starts an alternate cancer therapy prior to progression. This analysis uses tumour measurements and assessments provided on the eCRFs.	
Comparison groups	Cediranib 20 mg v Bevacizumab 5 mg/kg
Number of subjects included in analysis	1422
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0925
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.98
upper limit	1.25

Statistical analysis title	Sensitivity (Interval censored approach)
Statistical analysis description:	
The proportion of patients progressing was compared in discrete time intervals after randomisation. The analysis uses a binary model with a complementary log-log link function so that the results could be approximated as a HR. An adjusted analysis was performed allowing for the effect of treatment and the same covariates used for the primary analysis. Treatment comparisons was summarised using the estimated HR from the adjusted binary analysis together with its 95% CI.	
Comparison groups	Cediranib 20 mg v Bevacizumab 5 mg/kg

Number of subjects included in analysis	1422
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0912 ^[1]
Method	Binary model
Parameter estimate	Hazard ratio (HR)
Point estimate	1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.98
upper limit	1.27

Notes:

[1] - Method: Binary model with complementary log-log link function

Statistical analysis title	Sensitivity (Central review)
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Statistical analysis description:

A supportive analysis was performed using the tumour assessment data provided by an independent central review. When calculating PFS, the progression date is the date determined by the central review, based upon the visit responses provided by the central review, and following programmatic incorporation of the same censoring mechanism as applied to the primary PFS analysis. The date of progression is assumed as the earliest tumour assessment date associated with that visit.

Comparison groups	Cediranib 20 mg v Bevacizumab 5 mg/kg
Number of subjects included in analysis	1422
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.5641
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.2

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description:	
Number of months from randomisation to the date of death from any cause	
End point type	Secondary
End point timeframe:	
Baseline through to date of death	

End point values	Cediranib 20 mg	Bevacizumab 5 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	709	713		
Units: Months				
median (inter-quartile range (Q1-Q3))	22.8 (13.3 to 32.3)	21.3 (12.2 to 32.8)		

Statistical analyses

Statistical analysis title	Overall survival
Statistical analysis description: The log-rank test was stratified by albumin, ALP, and permance status.	
Comparison groups	Cediranib 20 mg v Bevacizumab 5 mg/kg
Number of subjects included in analysis	1422
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.5459
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.12

Secondary: Quality of Life (QoL) Questionnaires

End point title	Quality of Life (QoL) Questionnaires
End point description:	
End point type	Secondary
End point timeframe:	
Till data-cut off	

End point values	Cediranib 20 mg	Bevacizumab 5 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	709	713		
Units: Days				
median (inter-quartile range (Q1-Q3))	170 (56 to 328)	245 (112 to 348)		

Statistical analyses

Statistical analysis title	Time to worsening (FCSI 9-item)
Statistical analysis description: Uses same methodology as PFS analysis.	
Comparison groups	Cediranib 20 mg v Bevacizumab 5 mg/kg
Number of subjects included in analysis	1422
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.2
upper limit	1.56

Statistical analysis title	Time to worsening (FCSI 7-item)
Statistical analysis description: Uses same methodology as PFS analysis.	
Comparison groups	Cediranib 20 mg v Bevacizumab 5 mg/kg
Number of subjects included in analysis	1422
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.26
upper limit	1.65

Secondary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)
End point description:	
End point type	Secondary
End point timeframe: RECIST assessed at baseline, then at 8 weekly intervals for 24 weeks, and then every 12 weeks thereafter through to progression or data cut off date of 15/11/09 whichever was earliest.	

End point values	Cediranib 20 mg	Bevacizumab 5 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	709	713		
Units: Responses				
Responders	328	337		
Stable disease	259	268		
Progressive disease	82	79		
Non-evaluable	40	29		

Statistical analyses

Statistical analysis title	Best Objective Response (ORR)
Statistical analysis description:	
An Odds Ratio of greater than 1 favours cediranib.	
Odds ratio, p-value and confidence interval estimated from a logistic regression model including factors for	
treatment, Baseline Albumin (<4 and >= 4 g/dl), ALP (<= 160 and >160 u/L) & WHO Performance status (0 or 1/2). For baseline albumin, ALP and WHO performance status, if a baseline value is not available, the strata from the IVRS randomization was assumed	
Comparison groups	Cediranib 20 mg v Bevacizumab 5 mg/kg
Number of subjects included in analysis	1422
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.6719
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	1.18

Secondary: Duration of Response (DoR)

End point title	Duration of Response (DoR)
End point description:	
End point type	Secondary
End point timeframe:	
RECIST assessed at baseline, week 1, 2, 4, 6, 8, 12 and then every 4 weeks thereafter through to progression or data cut off date of 15/11/09 whichever was earliest.	

End point values	Cediranib 20 mg	Bevacizumab 5 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	709	713		
Units: Months				
median (inter-quartile range (Q1-Q3))	8.6 (6.1 to 12.1)	9.6 (6.5 to 13.6)		

Statistical analyses

Statistical analysis title	Duration of response (EDoR)
Statistical analysis description:	
To provide a more robust assessment of duration of response the Expected Duration of Response (EDoR) was analysed.	
This method combines information of the response rate, based on the entire ITT population, with information based on the duration of response in responding patients, through a simple mixture distribution to calculate the expected duration of response	
Comparison groups	Cediranib 20 mg v Bevacizumab 5 mg/kg
Number of subjects included in analysis	1422
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.2021
Method	EDoR (Ellis et al 2008)
Parameter estimate	Ratio of EDoR
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	1.05

Secondary: Rate of resection of liver metastases

End point title	Rate of resection of liver metastases
End point description:	
The rate of resection will be analyzed using logistic regression, adjusting for the same baseline covariates as PFS, with the addition of a factor for liver only involvement at baseline (patients with only liver involvement at baseline will be assigned a value of 1, while patients with liver involvement and at least one other site of disease will be assigned a value of 0).	
End point type	Secondary
End point timeframe:	
Till data-cut off	

End point values	Cediranib 20 mg	Bevacizumab 5 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	709	713		
Units: Patient (n)				
Patients undergoing liver resection	31	37		

Statistical analyses

Statistical analysis title	Rate of resection (odds ratio)
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Statistical analysis description:

The rate of resection will be analyzed using logistic regression, adjusting for the same baseline covariates as PFS, with the addition of a factor for liver only involvement at baseline (patients with only liver involvement at baseline will be assigned a value of 1, while patients with liver involvement and at least one other site of disease will be assigned a value of 0).

Comparison groups	Cediranib 20 mg v Bevacizumab 5 mg/kg
Number of subjects included in analysis	1422
Analysis specification	Pre-specified
Analysis type	superiority ^[2]
P-value	< 0.6368
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	1.46

Notes:

[2] - An Odds Ratio of greater than 1 favours cediranib. Subset of patients undergoing liver resection.

Statistical analysis title	Rate of resection (odds ratio)
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Statistical analysis description:

The rate of resection will be analyzed using logistic regression, adjusting for the same baseline covariates as PFS, with the addition of a factor for liver only involvement at baseline (patients with only liver involvement at baseline will be assigned a value of 1, while patients with liver involvement and at least one other site of disease will be assigned a value of 0).

Comparison groups	Cediranib 20 mg v Bevacizumab 5 mg/kg
Number of subjects included in analysis	1422
Analysis specification	Pre-specified
Analysis type	superiority ^[3]
P-value	< 0.2133
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	3.39

Notes:

[3] - An Odds Ratio of greater than 1 favours cediranib. Subset of patients undergoing liver resection with no remaining sites of disease on RECIST scan following resection.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug until last study visit

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17
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Reporting groups

Reporting group title	FOLFOX + bevacizumab 5mg/kg
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Reporting group description: -

Reporting group title	FOLFOX + cediranib 20mg
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Reporting group description: -

Reporting group title	FOLFOX + cediranib 30mg
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Reporting group description: -

Serious adverse events	FOLFOX + bevacizumab 5mg/kg	FOLFOX + cediranib 20mg	FOLFOX + cediranib 30mg
Total subjects affected by serious adverse events			
subjects affected / exposed	231 / 704 (32.81%)	275 / 705 (39.01%)	90 / 192 (46.88%)
number of deaths (all causes)	246	238	105
number of deaths resulting from adverse events	13	9	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
METASTATIC PAIN			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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
OSTEOMA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TUMOUR HAEMORRHAGE			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	1 / 704 (0.14%)	1 / 705 (0.14%)	0 / 192 (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
TUMOUR PAIN			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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
Vascular disorders			
ARTERIAL THROMBOSIS LIMB			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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
CIRCULATORY COLLAPSE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEEP VEIN THROMBOSIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	9 / 704 (1.28%)	9 / 705 (1.28%)	2 / 192 (1.04%)
occurrences causally related to treatment / all	8 / 9	6 / 10	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
EMBOLISM VENOUS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	0 / 705 (0.00%)	1 / 192 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMATOMA			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (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
HYPERTENSION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	2 / 704 (0.28%)	9 / 705 (1.28%)	4 / 192 (2.08%)
occurrences causally related to treatment / all	2 / 2	10 / 10	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERTENSIVE CRISIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	2 / 705 (0.28%)	2 / 192 (1.04%)
occurrences causally related to treatment / all	0 / 0	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOTENSION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	2 / 704 (0.28%)	1 / 705 (0.14%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
JUGULAR VEIN THROMBOSIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	3 / 705 (0.43%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ORTHOSTATIC HYPOTENSION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	1 / 705 (0.14%)	0 / 192 (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
SHOCK HAEMORRHAGIC			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (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

SUBCLAVIAN VEIN THROMBOSIS alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	1 / 192 (0.52%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
THROMBOSIS alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	0 / 705 (0.00%)	1 / 192 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VASOSPASM alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (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
VENA CAVA THROMBOSIS alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	1 / 705 (0.14%)	1 / 192 (0.52%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VENOUS THROMBOSIS alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	1 / 705 (0.14%)	0 / 192 (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
VENOUS THROMBOSIS LIMB alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (0.00%)
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 ASTHENIA alternative dictionary used: MedDRA 17			

subjects affected / exposed	1 / 704 (0.14%)	3 / 705 (0.43%)	2 / 192 (1.04%)
occurrences causally related to treatment / all	0 / 1	3 / 3	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CATHETER RELATED COMPLICATION alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	2 / 705 (0.28%)	0 / 192 (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
CATHETER THROMBOSIS alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	2 / 705 (0.28%)	0 / 192 (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
CHILLS alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	2 / 705 (0.28%)	0 / 192 (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
DEATH alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	1 / 192 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
FATIGUE alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	6 / 705 (0.85%)	7 / 192 (3.65%)
occurrences causally related to treatment / all	0 / 0	6 / 7	5 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GENERAL PHYSICAL HEALTH DETERIORATION alternative dictionary used: MedDRA 17			

subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	1 / 192 (0.52%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
INFUSION SITE EXTRAVASATION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (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
INFUSION SITE INFLAMMATION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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
MALAISE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	3 / 705 (0.43%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MUCOSAL INFLAMMATION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (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
MULTI-ORGAN FAILURE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	2 / 705 (0.28%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
NON-CARDIAC CHEST PAIN			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	3 / 705 (0.43%)	2 / 192 (1.04%)
occurrences causally related to treatment / all	0 / 1	2 / 3	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

OEDEMA alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 704 (0.14%) 0 / 1 0 / 0	0 / 705 (0.00%) 0 / 0 0 / 0	0 / 192 (0.00%) 0 / 0 0 / 0
OEDEMA PERIPHERAL alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 704 (0.00%) 0 / 0 0 / 0	1 / 705 (0.14%) 0 / 1 0 / 0	0 / 192 (0.00%) 0 / 0 0 / 0
PAIN alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 704 (0.14%) 1 / 1 0 / 0	0 / 705 (0.00%) 0 / 0 0 / 0	0 / 192 (0.00%) 0 / 0 0 / 0
PYREXIA alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	11 / 704 (1.56%) 6 / 14 0 / 0	21 / 705 (2.98%) 13 / 26 0 / 0	9 / 192 (4.69%) 3 / 11 0 / 0
SUDDEN DEATH alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 704 (0.00%) 0 / 0 0 / 0	1 / 705 (0.14%) 1 / 1 1 / 1	0 / 192 (0.00%) 0 / 0 0 / 0
Immune system disorders DRUG HYPERSENSITIVITY alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	5 / 704 (0.71%) 5 / 5 0 / 0	2 / 705 (0.28%) 2 / 2 0 / 0	1 / 192 (0.52%) 2 / 2 0 / 0
FOOD ALLERGY alternative dictionary used: MedDRA 17			

subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERSENSITIVITY			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	2 / 704 (0.28%)	0 / 705 (0.00%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
FEMALE GENITAL TRACT FISTULA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	2 / 704 (0.28%)	0 / 705 (0.00%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FIBROCYSTIC BREAST DISEASE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
BRONCHOSPASM			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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
CHRONIC OBSTRUCTIVE PULMONARY DISEASE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	1 / 705 (0.14%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
DYSпноEA			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	4 / 704 (0.57%)	3 / 705 (0.43%)	2 / 192 (1.04%)
occurrences causally related to treatment / all	0 / 4	3 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
EPISTAXIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	2 / 705 (0.28%)	0 / 192 (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
HAEMOPTYSIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (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
LARYNGOSPASM			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	2 / 705 (0.28%)	0 / 192 (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
LUNG DISORDER			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
ORGANISING PNEUMONIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (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
PHARYNGEAL OEDEMA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	0 / 705 (0.00%)	1 / 192 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

PLEURAL EFFUSION alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 704 (0.00%) 0 / 0 0 / 0	1 / 705 (0.14%) 0 / 1 0 / 0	1 / 192 (0.52%) 0 / 1 0 / 0
PNEUMONIA ASPIRATION alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 704 (0.00%) 0 / 0 0 / 0	2 / 705 (0.28%) 0 / 2 0 / 1	0 / 192 (0.00%) 0 / 0 0 / 0
PNEUMOTHORAX alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	3 / 704 (0.43%) 2 / 3 0 / 0	0 / 705 (0.00%) 0 / 0 0 / 0	0 / 192 (0.00%) 0 / 0 0 / 0
PULMONARY EMBOLISM alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	21 / 704 (2.98%) 16 / 21 2 / 4	13 / 705 (1.84%) 11 / 15 0 / 0	6 / 192 (3.13%) 5 / 6 0 / 0
Psychiatric disorders BRADYPHRENIA alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 704 (0.00%) 0 / 0 0 / 0	0 / 705 (0.00%) 0 / 0 0 / 0	1 / 192 (0.52%) 0 / 1 0 / 0
DEPRESSION alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 704 (0.14%) 0 / 1 0 / 0	0 / 705 (0.00%) 0 / 0 0 / 0	0 / 192 (0.00%) 0 / 0 0 / 0
DISSOCIATIVE DISORDER alternative dictionary used: MedDRA 17			

subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUICIDAL IDEATION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	2 / 705 (0.28%)	0 / 192 (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
ASPARTATE AMINOTRANSFERASE INCREASED			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (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
BLOOD PRESSURE INCREASED			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	2 / 704 (0.28%)	2 / 705 (0.28%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	2 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BODY TEMPERATURE INCREASED			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (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
C-REACTIVE PROTEIN INCREASED			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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
ELECTROCARDIOGRAM QT PROLONGED			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (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
GAMMA-GLUTAMYLTRANSFERASE INCREASED			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (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
GLOMERULAR FILTRATION RATE DECREASED			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (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
HAEMOGLOBIN DECREASED			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (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
LIPASE INCREASED			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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
TRANSAMINASES INCREASED			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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
VIRAL TEST POSITIVE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
WEIGHT DECREASED			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (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
Injury, poisoning and procedural complications			
ABDOMINAL WOUND DEHISCENCE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CARDIAC VALVE REPLACEMENT COMPLICATION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
DRUG TOXICITY			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (0.00%)
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			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	1 / 704 (0.14%)	1 / 705 (0.14%)	0 / 192 (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
GASTROINTESTINAL STOMA COMPLICATION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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
HIP FRACTURE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
JOINT DISLOCATION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LUMBAR VERTEBRAL FRACTURE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MULTIPLE FRACTURES			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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
PATELLA FRACTURE			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
POST PROCEDURAL COMPLICATION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	3 / 705 (0.43%)	0 / 192 (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
POST PROCEDURAL HAEMORRHAGE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	1 / 705 (0.14%)	0 / 192 (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
PROCEDURAL PAIN			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
WOUND DEHISCENCE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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
WRIST FRACTURE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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			
DIHYDROPYRIMIDINE DEHYDROGENASE DEFICIENCY			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	1 / 704 (0.14%)	1 / 705 (0.14%)	0 / 192 (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
Cardiac disorders			
ACUTE MYOCARDIAL INFARCTION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	3 / 704 (0.43%)	1 / 705 (0.14%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	3 / 3	1 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
ANGINA PECTORIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	0 / 705 (0.00%)	1 / 192 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ANGINA UNSTABLE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (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
ARRHYTHMIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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
ARTERIOSPASM CORONARY			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (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
ATRIAL FIBRILLATION			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	2 / 704 (0.28%)	1 / 705 (0.14%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ATRIAL FLUTTER			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	0 / 705 (0.00%)	1 / 192 (0.52%)
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 THROMBOSIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	1 / 705 (0.14%)	0 / 192 (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
ATRIOVENTRICULAR BLOCK			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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
BRADYCARDIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (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
CARDIAC FAILURE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	3 / 705 (0.43%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 2	0 / 0
CARDIOMYOPATHY			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	0 / 705 (0.00%)	1 / 192 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

CARDIOPULMONARY FAILURE alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	1 / 192 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
CORONARY ARTERY DISEASE alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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
INTRACARDIAC THROMBUS alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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
LEFT VENTRICULAR DYSFUNCTION alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	1 / 192 (0.52%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LEFT VENTRICULAR FAILURE alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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
MITRAL VALVE INCOMPETENCE alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	0 / 705 (0.00%)	1 / 192 (0.52%)
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 alternative dictionary used: MedDRA 17			

subjects affected / exposed	1 / 704 (0.14%)	2 / 705 (0.28%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MYOCARDIAL ISCHAEMIA alternative dictionary used: MedDRA 17			
subjects affected / exposed	2 / 704 (0.28%)	3 / 705 (0.43%)	1 / 192 (0.52%)
occurrences causally related to treatment / all	2 / 2	1 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERICARDITIS CONSTRICTIVE alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUPRAVENTRICULAR TACHYCARDIA alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	0 / 705 (0.00%)	1 / 192 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders APHASIA alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (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
CEREBRAL HAEMORRHAGE alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	3 / 705 (0.43%)	2 / 192 (1.04%)
occurrences causally related to treatment / all	1 / 1	3 / 3	2 / 2
deaths causally related to treatment / all	1 / 1	2 / 2	2 / 2
CEREBRAL INFARCTION alternative dictionary used: MedDRA 17			

subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (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
CEREBRAL ISCHAEMIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	1 / 705 (0.14%)	1 / 192 (0.52%)
occurrences causally related to treatment / all	0 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CEREBROVASCULAR ACCIDENT			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	1 / 192 (0.52%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COGNITIVE DISORDER			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	0 / 705 (0.00%)	1 / 192 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CONVULSION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	0 / 705 (0.00%)	2 / 192 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEPRESSED LEVEL OF CONSCIOUSNESS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	1 / 705 (0.14%)	0 / 192 (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
DIZZINESS			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FACIAL PALSY			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GRAND MAL CONVULSION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (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
HAEMORRHAGIC CEREBRAL INFARCTION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (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
HAEMORRHAGIC STROKE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	0 / 705 (0.00%)	1 / 192 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEADACHE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEMIPARESIS			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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
HYPERTENSIVE ENCEPHALOPATHY			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (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
ISCHAEMIC CEREBRAL INFARCTION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (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
LETHARGY			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	1 / 192 (0.52%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LOSS OF CONSCIOUSNESS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	1 / 705 (0.14%)	0 / 192 (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
NERVE ROOT LESION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NEUROPATHY PERIPHERAL			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	1 / 192 (0.52%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

PARTIAL SEIZURES			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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
PERONEAL NERVE PALSY			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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
REVERSIBLE POSTERIOR LEUKOENCEPHALOPATHY SYNDROME			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	1 / 705 (0.14%)	0 / 192 (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
SOMNOLENCE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (0.00%)
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			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	3 / 705 (0.43%)	1 / 192 (0.52%)
occurrences causally related to treatment / all	0 / 1	2 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TOXIC ENCEPHALOPATHY			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (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
TRANSIENT ISCHAEMIC ATTACK			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	1 / 704 (0.14%)	3 / 705 (0.43%)	1 / 192 (0.52%)
occurrences causally related to treatment / all	0 / 1	3 / 4	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VASCULAR ENCEPHALOPATHY			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	0 / 705 (0.00%)	1 / 192 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
AGRANULOCYTOSIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	1 / 192 (0.52%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ANAEMIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	3 / 704 (0.43%)	1 / 705 (0.14%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	2 / 3	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COAGULOPATHY			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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
DISSEMINATED INTRAVASCULAR COAGULATION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (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
FEBRILE NEUTROPENIA			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	13 / 704 (1.85%)	11 / 705 (1.56%)	1 / 192 (0.52%)
occurrences causally related to treatment / all	17 / 17	14 / 15	2 / 2
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
IDIOPATHIC THROMBOCYTOPENIC PURPURA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	2 / 704 (0.28%)	0 / 705 (0.00%)	0 / 192 (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
LEUKOPENIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (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
NEUTROPENIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	11 / 704 (1.56%)	8 / 705 (1.13%)	5 / 192 (2.60%)
occurrences causally related to treatment / all	10 / 11	7 / 8	5 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PANCYTOPENIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	1 / 192 (0.52%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
THROMBOCYTOPENIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	6 / 705 (0.85%)	1 / 192 (0.52%)
occurrences causally related to treatment / all	1 / 1	6 / 6	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
DEAFNESS			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (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
VERTIGO			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
DIPLOPIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (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
ULCERATIVE KERATITIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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
Gastrointestinal disorders			
ABDOMINAL PAIN			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	10 / 704 (1.42%)	9 / 705 (1.28%)	2 / 192 (1.04%)
occurrences causally related to treatment / all	3 / 10	1 / 9	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ABDOMINAL PAIN LOWER			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ABDOMINAL PAIN UPPER			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	3 / 704 (0.43%)	2 / 705 (0.28%)	2 / 192 (1.04%)
occurrences causally related to treatment / all	1 / 3	1 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ANAL FISSURE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ANAL FISTULA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	4 / 704 (0.57%)	0 / 705 (0.00%)	0 / 192 (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
ASCITES			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COLITIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	3 / 704 (0.43%)	0 / 705 (0.00%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COLONIC OBSTRUCTION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	4 / 704 (0.57%)	3 / 705 (0.43%)	1 / 192 (0.52%)
occurrences causally related to treatment / all	1 / 4	2 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

DIARRHOEA				
alternative dictionary used: MedDRA 17				
subjects affected / exposed	13 / 704 (1.85%)	30 / 705 (4.26%)	11 / 192 (5.73%)	
occurrences causally related to treatment / all	13 / 15	32 / 35	11 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0	
DUODENAL ULCER				
alternative dictionary used: MedDRA 17				
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (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	
DUODENAL ULCER PERFORATION				
alternative dictionary used: MedDRA 17				
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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	
DUODENITIS				
alternative dictionary used: MedDRA 17				
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0	
ENTERITIS				
alternative dictionary used: MedDRA 17				
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	1 / 192 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0	
ENTEROVESICAL FISTULA				
alternative dictionary used: MedDRA 17				
subjects affected / exposed	1 / 704 (0.14%)	1 / 705 (0.14%)	0 / 192 (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	
GASTRIC ULCER HAEMORRHAGE				
alternative dictionary used: MedDRA 17				

subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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
GASTRITIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	1 / 705 (0.14%)	0 / 192 (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
GASTROINTESTINAL HAEMORRHAGE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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 INFLAMMATION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	0 / 705 (0.00%)	1 / 192 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROINTESTINAL PAIN			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	0 / 705 (0.00%)	1 / 192 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROINTESTINAL TOXICITY			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	0 / 705 (0.00%)	1 / 192 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROOESOPHAGEAL REFLUX DISEASE			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	2 / 704 (0.28%)	0 / 705 (0.00%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ILEUS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	6 / 704 (0.85%)	7 / 705 (0.99%)	2 / 192 (1.04%)
occurrences causally related to treatment / all	0 / 6	2 / 7	1 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
ILEUS PARALYTIC			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	0 / 705 (0.00%)	1 / 192 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INGUINAL HERNIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	0 / 705 (0.00%)	1 / 192 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INTESTINAL OBSTRUCTION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	12 / 704 (1.70%)	9 / 705 (1.28%)	2 / 192 (1.04%)
occurrences causally related to treatment / all	3 / 12	3 / 9	1 / 2
deaths causally related to treatment / all	1 / 1	0 / 1	0 / 0
INTESTINAL PERFORATION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	6 / 704 (0.85%)	0 / 705 (0.00%)	1 / 192 (0.52%)
occurrences causally related to treatment / all	3 / 6	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

LARGE INTESTINAL HAEMORRHAGE alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 704 (0.14%) 1 / 1 0 / 0	0 / 705 (0.00%) 0 / 0 0 / 0	0 / 192 (0.00%) 0 / 0 0 / 0
LARGE INTESTINAL OBSTRUCTION alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 704 (0.14%) 0 / 1 0 / 0	1 / 705 (0.14%) 0 / 1 0 / 0	1 / 192 (0.52%) 0 / 1 0 / 0
LARGE INTESTINE PERFORATION alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 704 (0.14%) 1 / 1 0 / 0	1 / 705 (0.14%) 0 / 1 0 / 0	1 / 192 (0.52%) 1 / 1 0 / 0
MELAENA alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 704 (0.14%) 1 / 1 0 / 0	1 / 705 (0.14%) 1 / 1 0 / 0	0 / 192 (0.00%) 0 / 0 0 / 0
MESENTERIC ARTERY THROMBOSIS alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 704 (0.00%) 0 / 0 0 / 0	1 / 705 (0.14%) 1 / 1 1 / 1	0 / 192 (0.00%) 0 / 0 0 / 0
MOUTH ULCERATION alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 704 (0.00%) 0 / 0 0 / 0	1 / 705 (0.14%) 1 / 1 0 / 0	0 / 192 (0.00%) 0 / 0 0 / 0
NAUSEA alternative dictionary used: MedDRA 17			

subjects affected / exposed	4 / 704 (0.57%)	10 / 705 (1.42%)	1 / 192 (0.52%)
occurrences causally related to treatment / all	4 / 4	9 / 10	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OESOPHAGEAL VARICES HAEMORRHAGE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (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
OESOPHAGITIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	0 / 705 (0.00%)	1 / 192 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PANCREATITIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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
PANCREATITIS ACUTE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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
PERIPROCTITIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERITONITIS			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	1 / 704 (0.14%)	1 / 705 (0.14%)	0 / 192 (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
PROCTALGIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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
RECTAL HAEMORRHAGE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	5 / 705 (0.71%)	1 / 192 (0.52%)
occurrences causally related to treatment / all	0 / 0	4 / 6	1 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
RECTAL PERFORATION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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
REFLUX OESOPHAGITIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (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
SMALL INTESTINAL OBSTRUCTION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	7 / 704 (0.99%)	7 / 705 (0.99%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	2 / 7	2 / 8	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
STOMATITIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	7 / 705 (0.99%)	2 / 192 (1.04%)
occurrences causally related to treatment / all	1 / 1	8 / 8	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

SUBILEUS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	3 / 705 (0.43%)	0 / 192 (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
VARICES OESOPHAGEAL			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VOMITING			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	12 / 704 (1.70%)	11 / 705 (1.56%)	3 / 192 (1.56%)
occurrences causally related to treatment / all	10 / 12	10 / 11	2 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
BILE DUCT OBSTRUCTION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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
CHOLECYSTITIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	1 / 705 (0.14%)	0 / 192 (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
HEPATIC FAILURE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (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
HEPATIC PAIN			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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
HYPERBILIRUBINAEMIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	2 / 705 (0.28%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PORTAL VEIN THROMBOSIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	2 / 705 (0.28%)	0 / 192 (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
Skin and subcutaneous tissue disorders			
DERMATITIS CONTACT			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (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
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	0 / 705 (0.00%)	2 / 192 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUBCUTANEOUS EMPHYSEMA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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
SWELLING FACE			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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
Renal and urinary disorders			
BLADDER OBSTRUCTION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMATURIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	1 / 192 (0.52%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYDRONEPHROSIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	2 / 704 (0.28%)	0 / 705 (0.00%)	0 / 192 (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
RENAL COLIC			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (0.00%)
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			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	2 / 705 (0.28%)	1 / 192 (0.52%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RENAL FAILURE ACUTE			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RENAL PAIN			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (0.00%)
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			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	1 / 705 (0.14%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY INCONTINENCE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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 RETENTION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	1 / 705 (0.14%)	0 / 192 (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
Endocrine disorders			
ADRENAL INSUFFICIENCY			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (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
HYPOTHYROIDISM			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	1 / 192 (0.52%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
BACK PAIN			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	3 / 704 (0.43%)	2 / 705 (0.28%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHONDROCALCINOSIS PYROPHOSPHATE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FLANK PAIN			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INTERVERTEBRAL DISC PROTRUSION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MUSCULOSKELETAL PAIN			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (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
MYALGIA			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	0 / 704 (0.00%)	0 / 705 (0.00%)	1 / 192 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NECK PAIN			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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
OSTEOPOROSIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	1 / 705 (0.14%)	0 / 192 (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
PATHOLOGICAL FRACTURE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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
PERIOSTITIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
ABDOMINAL ABSCESS			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	0 / 704 (0.00%)	0 / 705 (0.00%)	1 / 192 (0.52%)
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 INFECTION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	0 / 705 (0.00%)	1 / 192 (0.52%)
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 SEPSIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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
ABSCESS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	2 / 704 (0.28%)	0 / 705 (0.00%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ANAL ABSCESS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	2 / 705 (0.28%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
APPENDICITIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	1 / 192 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BREAST ABSCESS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (0.00%)
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 alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 704 (0.14%) 0 / 1 0 / 0	1 / 705 (0.14%) 1 / 1 0 / 0	1 / 192 (0.52%) 0 / 1 0 / 0
BRONCHOPNEUMONIA alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 704 (0.00%) 0 / 0 0 / 0	1 / 705 (0.14%) 0 / 1 0 / 0	0 / 192 (0.00%) 0 / 0 0 / 0
CATHETER RELATED INFECTION alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	6 / 704 (0.85%) 2 / 6 0 / 0	6 / 705 (0.85%) 2 / 6 0 / 0	1 / 192 (0.52%) 0 / 1 0 / 0
CATHETER SEPSIS alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	3 / 704 (0.43%) 2 / 3 0 / 0	1 / 705 (0.14%) 0 / 1 0 / 0	0 / 192 (0.00%) 0 / 0 0 / 0
CATHETER SITE CELLULITIS alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 704 (0.00%) 0 / 0 0 / 0	1 / 705 (0.14%) 1 / 1 0 / 0	1 / 192 (0.52%) 1 / 1 0 / 0
CELLULITIS alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 704 (0.14%) 0 / 1 0 / 0	1 / 705 (0.14%) 0 / 1 0 / 0	0 / 192 (0.00%) 0 / 0 0 / 0
CENTRAL LINE INFECTION alternative dictionary used: MedDRA 17			

subjects affected / exposed	4 / 704 (0.57%)	4 / 705 (0.57%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	3 / 4	2 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CLOSTRIDIAL INFECTION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	1 / 705 (0.14%)	0 / 192 (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
DIVERTICULITIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	2 / 704 (0.28%)	0 / 705 (0.00%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ENDOCARDITIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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
ENTEROCOCCAL INFECTION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GAS GANGRENE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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

GASTROENTERITIS alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	2 / 704 (0.28%) 0 / 2 0 / 0	2 / 705 (0.28%) 2 / 2 0 / 0	0 / 192 (0.00%) 0 / 0 0 / 0
GASTROENTERITIS VIRAL alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 704 (0.14%) 0 / 1 0 / 0	0 / 705 (0.00%) 0 / 0 0 / 0	0 / 192 (0.00%) 0 / 0 0 / 0
GINGIVAL INFECTION alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 704 (0.14%) 0 / 1 0 / 0	0 / 705 (0.00%) 0 / 0 0 / 0	0 / 192 (0.00%) 0 / 0 0 / 0
HEPATITIS C alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 704 (0.00%) 0 / 0 0 / 0	1 / 705 (0.14%) 0 / 1 0 / 0	0 / 192 (0.00%) 0 / 0 0 / 0
HERPES VIRUS INFECTION alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 704 (0.00%) 0 / 0 0 / 0	1 / 705 (0.14%) 0 / 1 0 / 0	0 / 192 (0.00%) 0 / 0 0 / 0
HERPES ZOSTER alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	2 / 704 (0.28%) 0 / 2 0 / 0	0 / 705 (0.00%) 0 / 0 0 / 0	0 / 192 (0.00%) 0 / 0 0 / 0
INFECTION alternative dictionary used: MedDRA 17			

subjects affected / exposed	1 / 704 (0.14%)	4 / 705 (0.57%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INFLUENZA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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
INFUSION SITE INFECTION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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
LIVER ABSCESS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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
LOBAR PNEUMONIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	1 / 192 (0.52%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LOWER RESPIRATORY TRACT INFECTION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	3 / 704 (0.43%)	1 / 705 (0.14%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LUNG INFECTION			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (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
MUCORMYCOSIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
NASOPHARYNGITIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	0 / 705 (0.00%)	1 / 192 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NECROTISING FASCIITIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
NEUTROPENIC SEPSIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	0 / 705 (0.00%)	1 / 192 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
OESOPHAGEAL CANDIDIASIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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
PELVIC ABSCESS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (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

PERIRECTAL ABSCESS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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
PNEUMONIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	5 / 704 (0.71%)	10 / 705 (1.42%)	2 / 192 (1.04%)
occurrences causally related to treatment / all	2 / 5	6 / 10	0 / 2
deaths causally related to treatment / all	1 / 1	1 / 1	0 / 0
PULMONARY TUBERCULOSIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	1 / 192 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYELONEPHRITIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RESPIRATORY TRACT INFECTION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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
RETROPERITONEAL ABSCESS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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
SEPSIS			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	6 / 704 (0.85%)	6 / 705 (0.85%)	1 / 192 (0.52%)
occurrences causally related to treatment / all	1 / 6	4 / 6	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
SEPTIC SHOCK			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	2 / 704 (0.28%)	1 / 705 (0.14%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 1	0 / 0
SINUSITIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	2 / 704 (0.28%)	0 / 705 (0.00%)	0 / 192 (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
STAPHYLOCOCCAL INFECTION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	2 / 704 (0.28%)	1 / 705 (0.14%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TOOTH ABSCESS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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
UPPER RESPIRATORY TRACT INFECTION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	1 / 705 (0.14%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY TRACT INFECTION			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	3 / 704 (0.43%)	6 / 705 (0.85%)	1 / 192 (0.52%)
occurrences causally related to treatment / all	0 / 4	2 / 6	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
UROSEPSIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	1 / 705 (0.14%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
VIRAL DIARRHOEA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VIRAL INFECTION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
WOUND INFECTION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
DECREASED APPETITE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	2 / 705 (0.28%)	2 / 192 (1.04%)
occurrences causally related to treatment / all	0 / 0	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEHYDRATION			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	8 / 704 (1.14%)	6 / 705 (0.85%)	5 / 192 (2.60%)
occurrences causally related to treatment / all	7 / 8	4 / 7	2 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ELECTROLYTE IMBALANCE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (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
FLUID INTAKE REDUCED			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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
GOUT			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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
HYPERCALCAEMIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	0 / 705 (0.00%)	1 / 192 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERGLYCAEMIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	3 / 704 (0.43%)	0 / 705 (0.00%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERKALAEMIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

HYPOALBUMINAEMIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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
HYPOCALCAEMIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (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
HYPOGLYCAEMIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	1 / 705 (0.14%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOKALAEMIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	4 / 705 (0.57%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	0 / 1	3 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPONATRAEMIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 704 (0.00%)	2 / 705 (0.28%)	0 / 192 (0.00%)
occurrences causally related to treatment / all	0 / 0	4 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
KETOACIDOSIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 704 (0.14%)	0 / 705 (0.00%)	0 / 192 (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

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

Non-serious adverse events	FOLFOX + bevacizumab 5mg/kg	FOLFOX + cediranib 20mg	FOLFOX + cediranib 30mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	672 / 704 (95.45%)	684 / 705 (97.02%)	187 / 192 (97.40%)
Vascular disorders			
HYPERTENSION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	183 / 704 (25.99%)	292 / 705 (41.42%)	92 / 192 (47.92%)
occurrences (all)	246	382	134
PHLEBITIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	31 / 704 (4.40%)	22 / 705 (3.12%)	10 / 192 (5.21%)
occurrences (all)	35	23	10
General disorders and administration site conditions			
ASTHENIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	73 / 704 (10.37%)	96 / 705 (13.62%)	31 / 192 (16.15%)
occurrences (all)	161	175	66
FATIGUE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	299 / 704 (42.47%)	314 / 705 (44.54%)	89 / 192 (46.35%)
occurrences (all)	493	645	144
OEDEMA PERIPHERAL			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	39 / 704 (5.54%)	28 / 705 (3.97%)	14 / 192 (7.29%)
occurrences (all)	49	33	15
PYREXIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	123 / 704 (17.47%)	92 / 705 (13.05%)	26 / 192 (13.54%)
occurrences (all)	174	128	43
Immune system disorders			
DRUG HYPERSENSITIVITY			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	50 / 704 (7.10%)	41 / 705 (5.82%)	10 / 192 (5.21%)
occurrences (all)	75	54	16
Respiratory, thoracic and mediastinal			

disorders			
COUGH			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	68 / 704 (9.66%)	71 / 705 (10.07%)	22 / 192 (11.46%)
occurrences (all)	81	80	27
DYSPHONIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	81 / 704 (11.51%)	124 / 705 (17.59%)	47 / 192 (24.48%)
occurrences (all)	105	164	68
DYSPNOEA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	43 / 704 (6.11%)	60 / 705 (8.51%)	27 / 192 (14.06%)
occurrences (all)	53	76	36
EPISTAXIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	172 / 704 (24.43%)	169 / 705 (23.97%)	45 / 192 (23.44%)
occurrences (all)	261	224	71
OROPHARYNGEAL PAIN			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	37 / 704 (5.26%)	44 / 705 (6.24%)	13 / 192 (6.77%)
occurrences (all)	46	47	14
Psychiatric disorders			
DEPRESSION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	23 / 704 (3.27%)	23 / 705 (3.26%)	11 / 192 (5.73%)
occurrences (all)	23	24	11
INSOMNIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	55 / 704 (7.81%)	49 / 705 (6.95%)	16 / 192 (8.33%)
occurrences (all)	64	55	17
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	13 / 704 (1.85%)	18 / 705 (2.55%)	11 / 192 (5.73%)
occurrences (all)	16	25	14

WEIGHT DECREASED alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences (all)	56 / 704 (7.95%) 59	80 / 705 (11.35%) 83	32 / 192 (16.67%) 35
Nervous system disorders			
DIZZINESS alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences (all)	33 / 704 (4.69%) 34	51 / 705 (7.23%) 65	16 / 192 (8.33%) 21
DYSGEUSIA alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences (all)	84 / 704 (11.93%) 106	82 / 705 (11.63%) 109	24 / 192 (12.50%) 35
HEADACHE alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences (all)	90 / 704 (12.78%) 179	117 / 705 (16.60%) 182	46 / 192 (23.96%) 68
LETHARGY alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences (all)	30 / 704 (4.26%) 49	40 / 705 (5.67%) 59	12 / 192 (6.25%) 20
NEUROPATHY PERIPHERAL alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences (all)	212 / 704 (30.11%) 337	218 / 705 (30.92%) 433	49 / 192 (25.52%) 68
PARAESTHESIA alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences (all)	158 / 704 (22.44%) 319	157 / 705 (22.27%) 301	46 / 192 (23.96%) 101
PERIPHERAL SENSORY NEUROPATHY alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences (all)	144 / 704 (20.45%) 245	135 / 705 (19.15%) 224	37 / 192 (19.27%) 58
Blood and lymphatic system disorders			

ANAEMIA alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences (all)	79 / 704 (11.22%) 93	50 / 705 (7.09%) 67	16 / 192 (8.33%) 19
LEUKOPENIA alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences (all)	52 / 704 (7.39%) 88	56 / 705 (7.94%) 102	20 / 192 (10.42%) 30
NEUTROPENIA alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences (all)	228 / 704 (32.39%) 516	302 / 705 (42.84%) 674	85 / 192 (44.27%) 167
THROMBOCYTOPENIA alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences (all)	85 / 704 (12.07%) 150	186 / 705 (26.38%) 325	55 / 192 (28.65%) 104
Gastrointestinal disorders ABDOMINAL PAIN alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences (all)	124 / 704 (17.61%) 157	161 / 705 (22.84%) 217	49 / 192 (25.52%) 77
ABDOMINAL PAIN UPPER alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences (all)	59 / 704 (8.38%) 81	82 / 705 (11.63%) 109	21 / 192 (10.94%) 27
CONSTIPATION alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences (all)	187 / 704 (26.56%) 265	145 / 705 (20.57%) 256	34 / 192 (17.71%) 64
DIARRHOEA alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences (all)	354 / 704 (50.28%) 817	486 / 705 (68.94%) 1541	147 / 192 (76.56%) 475
DRY MOUTH alternative dictionary used: MedDRA 17			

subjects affected / exposed	30 / 704 (4.26%)	33 / 705 (4.68%)	10 / 192 (5.21%)
occurrences (all)	37	39	12
DYSPEPSIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	56 / 704 (7.95%)	45 / 705 (6.38%)	11 / 192 (5.73%)
occurrences (all)	81	60	14
DYSPHAGIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	10 / 704 (1.42%)	22 / 705 (3.12%)	11 / 192 (5.73%)
occurrences (all)	13	25	11
NAUSEA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	349 / 704 (49.57%)	355 / 705 (50.35%)	100 / 192 (52.08%)
occurrences (all)	883	888	199
STOMATITIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	187 / 704 (26.56%)	252 / 705 (35.74%)	77 / 192 (40.10%)
occurrences (all)	332	369	145
VOMITING			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	192 / 704 (27.27%)	221 / 705 (31.35%)	64 / 192 (33.33%)
occurrences (all)	380	394	121
Skin and subcutaneous tissue disorders			
ALOPECIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	64 / 704 (9.09%)	65 / 705 (9.22%)	18 / 192 (9.38%)
occurrences (all)	68	70	19
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	68 / 704 (9.66%)	104 / 705 (14.75%)	31 / 192 (16.15%)
occurrences (all)	81	138	50
RASH			
alternative dictionary used: MedDRA 17			

subjects affected / exposed occurrences (all)	38 / 704 (5.40%) 48	51 / 705 (7.23%) 62	14 / 192 (7.29%) 18
Renal and urinary disorders PROTEINURIA alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences (all)	40 / 704 (5.68%) 59	48 / 705 (6.81%) 83	23 / 192 (11.98%) 27
Endocrine disorders HYPOTHYROIDISM alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences (all)	8 / 704 (1.14%) 8	35 / 705 (4.96%) 36	24 / 192 (12.50%) 25
Musculoskeletal and connective tissue disorders ARTHRALGIA alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences (all) BACK PAIN alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences (all) MUSCULOSKELETAL PAIN alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences (all) MYALGIA alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences (all) PAIN IN EXTREMITY alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences (all)	40 / 704 (5.68%) 45 63 / 704 (8.95%) 78 35 / 704 (4.97%) 39 22 / 704 (3.13%) 28 38 / 704 (5.40%) 45	34 / 705 (4.82%) 40 54 / 705 (7.66%) 68 40 / 705 (5.67%) 49 18 / 705 (2.55%) 18 46 / 705 (6.52%) 55	15 / 192 (7.81%) 17 20 / 192 (10.42%) 27 7 / 192 (3.65%) 8 11 / 192 (5.73%) 12 16 / 192 (8.33%) 19
Infections and infestations			

<p>NASOPHARYNGITIS</p> <p>alternative dictionary used: MedDRA 17</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>50 / 704 (7.10%)</p> <p>66</p>	<p>42 / 705 (5.96%)</p> <p>48</p>	<p>21 / 192 (10.94%)</p> <p>27</p>
<p>UPPER RESPIRATORY TRACT INFECTION</p> <p>alternative dictionary used: MedDRA 17</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>36 / 704 (5.11%)</p> <p>43</p>	<p>18 / 705 (2.55%)</p> <p>20</p>	<p>4 / 192 (2.08%)</p> <p>4</p>
<p>URINARY TRACT INFECTION</p> <p>alternative dictionary used: MedDRA 17</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>43 / 704 (6.11%)</p> <p>63</p>	<p>42 / 705 (5.96%)</p> <p>62</p>	<p>15 / 192 (7.81%)</p> <p>16</p>
<p>Metabolism and nutrition disorders</p> <p>DECREASED APPETITE</p> <p>alternative dictionary used: MedDRA 17</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>HYPOKALAEMIA</p> <p>alternative dictionary used: MedDRA 17</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>160 / 704 (22.73%)</p> <p>251</p> <p>38 / 704 (5.40%)</p> <p>55</p>	<p>177 / 705 (25.11%)</p> <p>242</p> <p>59 / 705 (8.37%)</p> <p>87</p>	<p>71 / 192 (36.98%)</p> <p>109</p> <p>16 / 192 (8.33%)</p> <p>21</p>

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported