Clinical trial results:
A Randomized, Double-blind, Multicenter Phase 3 Study of Irinotecan, Folinic Acid, and 5-Fluorouracil (FOLFIRI) Plus Ramucirumab or Placebo in Patients With Metastatic Colorectal Carcinoma Progressive During or Following First-Line Combination Therapy With Bevacizumab, Oxaliplatin, and a Fluoropyrimidine

Summary

EudraCT number	2010-021037-32
Trial protocol	FI FR AT NL ES PT DE IT SE BE DK GR HU SI
Global end of trial date	20 June 2016

Results information

Result version number	v1 (current)
This version publication date	25 June 2017
First version publication date	25 June 2017

Trial information

Trial identification

Sponsor protocol code	I4T-MC-JVBB

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01183780
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Number: 13856

Notes:

Sponsors

Sponsor organisation name	Eli Lilly and Company
Sponsor organisation address	Lilly Corporate Center, Indianapolis, IN, United States, 46285
Public contact	Available Mon Fri 9 AM 5 PM EST, Eli Lilly and Company, 1 877CTLilly,
Scientific contact	Available Mon Fri 9 AM 5 PM EST, Eli Lilly and Company, 1 8772854559,

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	20 June 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 June 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to compare overall survival in participants with metastatic colorectal cancer treated with either ramucirumab and FOLFIRI or placebo and FOLFIRI.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 December 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 283
Country: Number of subjects enrolled	Portugal: 4
Country: Number of subjects enrolled	Taiwan: 11
Country: Number of subjects enrolled	Greece: 16
Country: Number of subjects enrolled	Spain: 111
Country: Number of subjects enrolled	Israel: 14
Country: Number of subjects enrolled	Italy: 37
Country: Number of subjects enrolled	India: 3
Country: Number of subjects enrolled	France: 27
Country: Number of subjects enrolled	Puerto Rico: 3
Country: Number of subjects enrolled	Australia: 35
Country: Number of subjects enrolled	Denmark: 11
Country: Number of subjects enrolled	Netherlands: 14
Country: Number of subjects enrolled	Korea, Republic of: 47
Country: Number of subjects enrolled	Finland: 12
Country: Number of subjects enrolled	Austria: 18
Country: Number of subjects enrolled	Czech Republic: 77
Country: Number of subjects enrolled	Hungary: 47
Country: Number of subjects enrolled	Argentina: 18
Country: Number of subjects enrolled	Belgium: 52

Country: Number of subjects enrolled	Brazil: 5
Country: Number of subjects enrolled	Romania: 33
Country: Number of subjects enrolled	Germany: 44
Country: Number of subjects enrolled	Japan: 136
Country: Number of subjects enrolled	Sweden: 14
Worldwide total number of subjects	1072
EEA total number of subjects	517

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)	645
From 65 to 84 years	425
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Completers included participants who died from any cause and participants who were alive and on study at conclusion however were off treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Ramucirumab + FOLFIRI

Arm description:

On Day 1 of each 14-day cycle, participants received ramucirumab followed by other study treatment in the following sequence: Irinotecan, Folinic Acid and 5-Fluorouracil (FOLFIRI). Treatment continued until disease progression, unacceptable toxicity, or other withdrawal criteria were met.
Ramucirumab: 8 milligrams/kilogram (mg/kg) administered intravenously.

Irinotecan: 180 mg/m^2 administered intravenously.

Folinic Acid: 400 mg/m^2 administered intravenously.

5-Fluorouracil: 400 mg/m^2 bolus immediately followed by
2400 mg/m^2 continuous infusion.

Arm type	Experimental
Investigational medicinal product name	Ramucirumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

8 milligrams/kilogram (mg/kg) administered intravenously.

Investigational medicinal product name	Irinotecan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

180 mg/m² administered intravenously.

Investigational medicinal product name	Folinic Acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

400 mg/m² administered intravenously.

Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

400 mg/m² bolus immediately followed by 2400 mg/m² continuous infusion.

Arm title	Placebo + FOLFIRI

Arm description:

On Day 1 of each 14-day cycle, participants received placebo followed by other study treatment in the following sequence: Irinotecan, Folinic Acid and 5-Fluorouracil. Treatment continued until disease progression, unacceptable toxicity, or other withdrawal criteria were met.

Placebo: Administered intravenously.

Irinotecan: 180 mg/m^2 administered intravenously.

Folinic Acid: 400 mg/m^2 administered intravenously.

5-Fluorouracil: 400 mg/m^2 bolus immediately followed by 2400 mg/m^2 continuous infusion.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered intravenously.

Investigational medicinal product name	Irinotecan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

180 mg/m² administered intravenously.

Investigational medicinal product name	Folinic Acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

400 mg/m² administered intravenously.

Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

8 milligrams/kilogram (mg/kg) administered intravenously.

Number of subjects in period 1	Ramucirumab + FOLFIRI	Placebo + FOLFIRI
Started	536	536
received at least 1 dose of study drug	528	529
Completed	505	511
Not completed	31	25
Consent withdrawn by subject	25	14
Lost to follow-up	6	11

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study
Reporting group description:	
Baseline Analysis Population: All randomized participants.	

Reporting group values	Overall Study	Total	
Number of subjects	1072	1072	
Age Categorical Units:			
Age Continuous Units: years			
median	62		
full range (min-max)	21 to 87	-	
Gender, Male/Female Units: Subjects			
Male	615	615	
Female	457	457	
Region of Enrollment Units: Subjects			
United States	283	283	
Portugal	4	4	
Taiwan	11	11	
Greece	16	16	
Spain	111	111	
Israel	14	14	
Italy	37	37	
India	3	3	
France	27	27	
Puerto Rico	3	3	
Australia	35	35	
Denmark	11	11	
Netherlands	14	14	
Korea, Republic of	47	47	
Finland	12	12	
Austria	18	18	
Czech Republic	77	77	
Hungary	47	47	
Argentina	18	18	
Belgium	52	52	
Brazil	5	5	
Romania	33	33	
Germany	44	44	
Japan	136	136	
Sweden	14	14	
Age, Categorical Units: Subjects			

<=18 years	0	0	
Between 18 and 65 years	645	645	
>=65 years	427	427	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	77	77	
Not Hispanic or Latino	469	469	
Unknown or Not Reported	526	526	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	1	
Asian	214	214	
Native Hawaiian or Other Pacific Islander	2	2	
Black or African American	30	30	
White	815	815	
More than one race	3	3	
Unknown or Not Reported	7	7	

End points

End points reporting groups

Reporting group title	Ramucirumab + FOLFIRI

Reporting group description:

On Day 1 of each 14-day cycle, participants received ramucirumab followed by other study treatment in the following sequence: Irinotecan, Folinic Acid and 5-Fluorouracil (FOLFIRI). Treatment continued until disease progression, unacceptable toxicity, or other withdrawal criteria were met.
Ramucirumab: 8 milligrams/kilogram (mg/kg) administered intravenously.

Irinotecan: 180 mg/m^2 administered intravenously.

Folinic Acid: 400 mg/m^2 administered intravenously.

5-Fluorouracil: 400 mg/m^2 bolus immediately followed by
2400 mg/m^2 continuous infusion.

Reporting group title	Placebo + FOLFIRI

Reporting group description:

On Day 1 of each 14-day cycle, participants received placebo followed by other study treatment in the following sequence: Irinotecan, Folinic Acid and 5-Fluorouracil. Treatment continued until disease progression, unacceptable toxicity, or other withdrawal criteria were met.

Placebo: Administered intravenously.

Irinotecan: 180 mg/m^2 administered intravenously.

Folinic Acid: 400 mg/m^2 administered intravenously.

5-Fluorouracil: 400 mg/m^2 bolus immediately followed by 2400 mg/m^2 continuous infusion.

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time in months from the date of randomization to the date of death from any cause. For participants not known to have died as of the cut-off date, OS was censored at the last known date alive.

Analysis Population Description : All randomized participants. Participants censored: Ramucirumab + FOLFIRI group = 164; Placebo + FOLFIRI= 139.

End point type	Primary

End point timeframe:

Randomization to Date of Death from Any Cause Up to 39.36 Months

End point values	Ramucirumab + FOLFIRI	Placebo + FOLFIRI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	536	536		
Units: months				
median (confidence interval 95%)	13.3 (12.4 to 14.5)	11.7 (10.8 to 12.7)		

Statistical analyses

Statistical analysis title	OS
Comparison groups	Ramucirumab + FOLFIRI v Placebo + FOLFIRI
Number of subjects included in analysis	1072
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.0219 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.844
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	0.976

Notes:

[1] - The analysis was performed on stratified data.

[2] - The analysis was performed on stratified data.

Secondary: Progression-free survival (PFS) time

End point title	Progression-free survival (PFS) time

End point description:

PFS was defined as the time from the date of randomization until the date of objectively determined progressive disease (PD) [according to Response Evaluation Criteria in Solid Tumors (RECIST) version (v). 1.1] or death due to any cause, whichever was first. PD is at least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 millimeters (mm). Participants who died without a reported prior progression were considered to have progressed on the day of their death. Participants who did not progress or were lost to follow-up were censored at the day of their last radiographic tumor assessment.

Analysis Population Description : All randomized participants. Participants censored: Ramucirumab + FOLFIRI = 60; Placebo + FOLFIRI = 42.

End point type	Secondary

End point timeframe:

Randomization to Measured PD or Date of Death from Any Cause Up to 38.01 Months

End point values	Ramucirumab + FOLFIRI	Placebo + FOLFIRI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	536	536		
Units: months				
median (confidence interval 95%)	5.7 (5.5 to 6.2)	4.5 (4.2 to 5.4)		

Statistical analyses

Statistical analysis title	PFS

Statistical analysis description:

Analysis was performed on stratified data.

Comparison groups	Ramucirumab + FOLFIRI v Placebo + FOLFIRI
Number of subjects included in analysis	1072
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.0005 [4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.793
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.697
upper limit	0.903

Notes:

[3] - Analysis was performed on stratified data.

[4] - Analysis was performed on stratified data.

Secondary: Percentage of participants achieving an objective response (objective response rate)

End point title	Percentage of participants achieving an objective response (objective response rate)

End point description:

The objective response rate is equal to the proportion of participants achieving a best overall response of partial response or complete response (PR + CR). Response was defined using RECIST, v. 1.1 criteria. CR was defined as the disappearance of all target and non-target lesions and any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm and normalization of tumor marker level of non-target lesions; PR was defined as having at least a 30% decrease in sum of longest diameter of target lesions taking as reference the baseline sum diameter.

Analysis Population Description : All randomized participants.

End point type	Secondary

End point timeframe:

Randomization until Disease Progression Up to 38.01 Months

End point values	Ramucirumab + FOLFIRI	Placebo + FOLFIRI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	536	536		
Units: percentage of participants				
number (confidence interval 95%)	13.4 (10.7 to 16.6)	12.5 (9.8 to 15.6)		

Statistical analyses

Statistical analysis title	Objective Response Rate
Comparison groups	Ramucirumab + FOLFIRI v Placebo + FOLFIRI
Number of subjects included in analysis	1072
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6336
Method	Cochran-Mantel-Haenszel

Secondary: Change From Baseline in EuroQol- 5D (EQ-5D)

End point title	Change From Baseline in EuroQol- 5D (EQ-5D)

End point description:

The EQ-5D is a generic, multidimensional, health status instrument. The profile allows participants to rate their health state in 5 health domains: mobility, self-care, usual activities, pain/discomfort, and mood using a 3-level scale (no problem, some problems, and major problems). These combinations of attributes were converted into a weighted health-state Index Score according to the United Kingdom (UK) population-based algorithm. The possible values for the Index Score ranged from -0.59 (severe problems in all 5 dimensions) to 1.0 (no problem in any dimension). A negative change indicated a worsening of the participant's health status.

Analysis Population Description : All randomized participants who had EQ-5D assessed at baseline and 30-day FU.

End point type	Secondary

End point timeframe:

Baseline and 30-Day Follow-Up (FU) up to 171 Weeks

End point values	Ramucirumab + FOLFIRI	Placebo + FOLFIRI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	308	310		
Units: units on a scale				
arithmetic mean (standard deviation)	-0.097 (± 0.279)	-0.103 (± 0.264)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Organisation for Research and Treatment of Cancer [EORTC] QLQ-C30 Global Health Status

End point title	Change From Baseline in European Organisation for Research and Treatment of Cancer [EORTC] QLQ-C30 Global Health Status

End point description:

The EORTC QLQ-C30 (v. 3.0) is a self-administered, cancer-specific questionnaire with multidimensional scales assessing 15 domains (5 functional domains, 9 symptoms, and global health status). A linear transformation was applied to standardize the raw scores to range between 0 and 100 per developer guidelines. For the functional domains and global health status scale, higher scores represent a better level of functioning. For symptom scales, higher scores represent a greater degree of symptoms. Maximum improvement is the best post-baseline change.

Analysis Population Description : All randomized participants who had EORTC QLQ-C30 assessed at baseline and post-baseline.

End point type	Secondary

End point timeframe:

Baseline Up to 171 Weeks

End point values	Ramucirumab + FOLFIRI	Placebo + FOLFIRI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	491	486		
Units: units on a scale				
arithmetic mean (standard deviation)	4 (± 20.61)	6.6 (± 18.84)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Treatment-Emergent Anti-Ramucirumab Antibodies

End point title	Percentage of Participants With Treatment-Emergent Anti-Ramucirumab Antibodies

End point description:

Blood samples were tested to determine if a participant reacted to ramucirumab by producing anti-ramucirumab antibodies. Samples were identified as treatment emergent anti-drug antibody (TE ADA) if the post-treatment sample had an increase of at least 4 fold in titer from pre-treatment values. If the pre-treatment value was not detected or was not present, a 1:20 post-treatment titer was required to indicate treatment emergence. The percentage of participants with TE ADA was calculated as: (the number of participants with TE ADA / total number of participants with at least 1 post-treatment immunogenicity sample analyzed)*100.

Analysis Population Description : All participants who received study treatment and who had immunogenicity samples analyzed at the specified time points.

End point type	Secondary

End point timeframe:

Cycles 1, 3, 5, and 30-Day FU

End point values	Ramucirumab + FOLFIRI	Placebo + FOLFIRI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	516[5]	512[6]		
Units: percentage of participants				
number (not applicable)				
Immunogenicity Any Time During Study	5.6	5.5		
Immunogenicity Post-Treatment	3.1	3.8		

Notes:

[5] - n=516 for Immunogenicity Any Time During Study.
n=47 for Immunogenicity Post-Treatment.
[6] - n=512 Immunogenicity Any Time During Study.
n=473 Immunogenicity Post-Treatment.

Statistical analyses

No statistical analyses for this end point

Secondary: Observed maximum concentration (Cmax) and observed minimum concentration (Cmin) of ramucirumab

End point title	Observed maximum concentration (Cmax) and observed minimum concentration (Cmin) of ramucirumab[7]

End point description:

All randomized participants who received at least one dose of study drug and had evaluable data for Cmin and Cmax.

End point type	Secondary

End point timeframe:

Preinfusion and 1 hour postinfusion in Cycles 3, 5, 9, 13, and 17

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetics data were only collected for participants in arm Ramucirumab + FOLFIRI.

End point values	Ramucirumab + FOLFIRI			
Subject group type	Reporting group			
Number of subjects analysed	248			
Units: micrograms/milliliter (ug/mL)				
geometric mean (geometric coefficient of variation)				
Cmin Dose 3	46.3 (± 45)			
Cmin Dose 5	65.1 (± 43)			
Cmin Dose 9	77.9 (± 51)			
Cmin Dose 13	75.9 (± 43)			
Cmin Dose 17	72 (± 49)			
Cmax Dose 3	221 (± 37)			
Cmax Dose 5	243 (± 39)			
Cmax Dose 9	262 (± 36)			
Cmax Dose 13	307 (± 33)			
Cmax Dose 17	253 (± 19)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Entire Study	
Adverse event reporting additional description:	
I4T-MC-JVBB	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups	
Reporting group title	FOLFIRI + Ramucirumab every 2 weeks
Reporting group description: -	
Reporting group title	FOLFIRI + Placebo every 2 weeks
Reporting group description: -	

Serious adverse events	FOLFIRI + Ramucirumab every 2 weeks	FOLFIRI + Placebo every 2 weeks	
Total subjects affected by serious adverse events			
subjects affected / exposed	198 / 529 (37.43%)	175 / 528 (33.14%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
colorectal cancer metastatic			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
malignant ascites			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
malignant pleural effusion			
alternative dictionary used: MedDRA 17.1			

subjects affected / exposed	0 / 529 (0.00%)	2 / 528 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
metastases to meninges			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
metastatic neoplasm			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
tumour haemorrhage			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
tumour pain			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
aortic dissection			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
deep vein thrombosis			
alternative dictionary used: MedDRA 17.1			

subjects affected / exposed	2 / 529 (0.38%)	3 / 528 (0.57%)	
occurrences causally related to treatment / all	1 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
embolism			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	2 / 529 (0.38%)	3 / 528 (0.57%)	
occurrences causally related to treatment / all	1 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypertension			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	4 / 529 (0.76%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypertensive crisis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypotension			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	2 / 529 (0.38%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypovolaemic shock			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
jugular vein thrombosis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	2 / 528 (0.38%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

lymphoedema			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
subclavian vein thrombosis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
thrombophlebitis superficial			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
vena cava embolism			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
venous thrombosis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	3 / 529 (0.57%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	2 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
cancer surgery			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
colostomy closure			
alternative dictionary used: MedDRA 17.1			

subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
enterostomy			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
high frequency ablation			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
asthenia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	4 / 529 (0.76%)	3 / 528 (0.57%)	
occurrences causally related to treatment / all	1 / 4	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
chest pain			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	3 / 528 (0.57%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
disease progression			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
fatigue			
alternative dictionary used: MedDRA 17.1			

subjects affected / exposed	5 / 529 (0.95%)	4 / 528 (0.76%)	
occurrences causally related to treatment / all	3 / 5	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
general physical health deterioration			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	3 / 529 (0.57%)	5 / 528 (0.95%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
hernia obstructive			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
malaise			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	3 / 529 (0.57%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
mucosal inflammation			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	4 / 529 (0.76%)	2 / 528 (0.38%)	
occurrences causally related to treatment / all	5 / 5	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
multi-organ failure			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
non-cardiac chest pain			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

oedema peripheral			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pyrexia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	4 / 529 (0.76%)	8 / 528 (1.52%)	
occurrences causally related to treatment / all	0 / 5	5 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
systemic inflammatory response syndrome			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	2 / 529 (0.38%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 2	0 / 0	
ulcer haemorrhage			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
anaphylactic reaction			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
drug hypersensitivity			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			

pelvic pain			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
chronic obstructive pulmonary disease			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	2 / 529 (0.38%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
dyspnoea			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	5 / 528 (0.95%)	
occurrences causally related to treatment / all	0 / 1	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
haemoptysis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
interstitial lung disease			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	2 / 528 (0.38%)	
occurrences causally related to treatment / all	3 / 3	2 / 2	
deaths causally related to treatment / all	1 / 1	0 / 0	
laryngeal inflammation			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
lung infiltration			
alternative dictionary used:			

MedDRA 17.1				
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)		
occurrences causally related to treatment / all	1 / 1	0 / 0		
deaths causally related to treatment / all	1 / 1	0 / 0		
pleural effusion				
alternative dictionary used: MedDRA 17.1				
subjects affected / exposed	1 / 529 (0.19%)	3 / 528 (0.57%)		
occurrences causally related to treatment / all	0 / 1	0 / 4		
deaths causally related to treatment / all	0 / 0	0 / 0		
pneumothorax				
alternative dictionary used: MedDRA 17.1				
subjects affected / exposed	1 / 529 (0.19%)	1 / 528 (0.19%)		
occurrences causally related to treatment / all	0 / 1	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
pneumothorax spontaneous				
alternative dictionary used: MedDRA 17.1				
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
pulmonary embolism				
alternative dictionary used: MedDRA 17.1				
subjects affected / exposed	10 / 529 (1.89%)	6 / 528 (1.14%)		
occurrences causally related to treatment / all	7 / 10	4 / 6		
deaths causally related to treatment / all	0 / 0	0 / 0		
pulmonary oedema				
alternative dictionary used: MedDRA 17.1				
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
respiratory arrest				
alternative dictionary used: MedDRA 17.1				

subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
respiratory distress			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
alcohol abuse			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
anxiety			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
confusional state			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
delirium			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
depression			
alternative dictionary used: MedDRA 17.1			

subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
disorientation			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
mental status changes			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	2 / 529 (0.38%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
suicide attempt			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Investigations			
alanine aminotransferase increased			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	2 / 528 (0.38%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
aspartate aminotransferase increased			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
blood bilirubin increased			
alternative dictionary used: MedDRA 17.1			

subjects affected / exposed	3 / 529 (0.57%)	2 / 528 (0.38%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
blood creatinine increased			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
blood culture positive			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
eastern cooperative oncology group performance status worsened			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
international normalised ratio increased			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	3 / 529 (0.57%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
neutrophil count decreased			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	2 / 529 (0.38%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
platelet count decreased			
alternative dictionary used: MedDRA 17.1			

subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
weight decreased			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
alcohol poisoning			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ankle fracture			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
compression fracture			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
fall			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	5 / 529 (0.95%)	2 / 528 (0.38%)	
occurrences causally related to treatment / all	1 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
femur fracture			
alternative dictionary used: MedDRA 17.1			

subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
fibula fracture			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hepatic haematoma			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hip fracture			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	2 / 529 (0.38%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
lower limb fracture			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
lumbar vertebral fracture			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
post procedural urine leak			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

procedural intestinal perforation			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
spinal fracture			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
stoma site haemorrhage			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
subdural haematoma			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
wound dehiscence			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
pyloric stenosis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
acute myocardial infarction			

alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
angina pectoris			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	2 / 529 (0.38%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
atrial fibrillation			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
atrial flutter			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
cardiac failure			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	2 / 529 (0.38%)	2 / 528 (0.38%)	
occurrences causally related to treatment / all	2 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 2	
cardio-respiratory arrest			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
congestive cardiomyopathy			
alternative dictionary used: MedDRA 17.1			

subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
myocardial infarction			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	3 / 528 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	1 / 2	
pericarditis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
right ventricular failure			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Nervous system disorders			
aphasia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
cerebral haematoma			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
cerebral ischaemia			
alternative dictionary used: MedDRA 17.1			

subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
cerebrovascular accident			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
dizziness			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	2 / 528 (0.38%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
dysarthria			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
epilepsy			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
headache			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hyperammonaemic encephalopathy			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

ischaemic stroke				
alternative dictionary used: MedDRA 17.1				
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
memory impairment				
alternative dictionary used: MedDRA 17.1				
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
optic neuritis				
alternative dictionary used: MedDRA 17.1				
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)		
occurrences causally related to treatment / all	1 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
posterior reversible encephalopathy syndrome				
alternative dictionary used: MedDRA 17.1				
subjects affected / exposed	1 / 529 (0.19%)	1 / 528 (0.19%)		
occurrences causally related to treatment / all	1 / 1	1 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
presyncope				
alternative dictionary used: MedDRA 17.1				
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
syncope				
alternative dictionary used: MedDRA 17.1				
subjects affected / exposed	1 / 529 (0.19%)	1 / 528 (0.19%)		
occurrences causally related to treatment / all	1 / 1	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
transient ischaemic attack				
alternative dictionary used: MedDRA 17.1				

subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
febrile neutropenia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	15 / 529 (2.84%)	8 / 528 (1.52%)	
occurrences causally related to treatment / all	14 / 16	7 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
leukopenia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
neutropenia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	6 / 529 (1.13%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	7 / 7	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
thrombocytopenia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	2 / 528 (0.38%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
thrombotic microangiopathy			
alternative dictionary used: MedDRA 17.1			

subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Eye disorders			
cataract			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
abdominal pain			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	10 / 529 (1.89%)	14 / 528 (2.65%)	
occurrences causally related to treatment / all	0 / 12	1 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
abdominal pain lower			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	2 / 528 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
abdominal pain upper			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	2 / 529 (0.38%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
anal fistula			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
anal haemorrhage			
alternative dictionary used: MedDRA 17.1			

subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
anal ulcer			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ascites			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	3 / 528 (0.57%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
colitis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	2 / 529 (0.38%)	2 / 528 (0.38%)	
occurrences causally related to treatment / all	1 / 2	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
constipation			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	2 / 529 (0.38%)	3 / 528 (0.57%)	
occurrences causally related to treatment / all	1 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
diarrhoea			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	19 / 529 (3.59%)	18 / 528 (3.41%)	
occurrences causally related to treatment / all	16 / 20	18 / 21	
deaths causally related to treatment / all	0 / 0	0 / 0	
dyspepsia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

enteritis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
enterocolitis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
gastric haemorrhage			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
gastritis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	3 / 529 (0.57%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	1 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
gastrointestinal inflammation			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
gastrointestinal perforation			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
haematemesis			
alternative dictionary used: MedDRA 17.1			

subjects affected / exposed	3 / 529 (0.57%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
haemorrhoidal haemorrhage			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hernial eventration			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ileus			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	3 / 529 (0.57%)	6 / 528 (1.14%)	
occurrences causally related to treatment / all	0 / 5	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 2	
incarcerated inguinal hernia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
inflammatory bowel disease			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
inguinal hernia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	2 / 529 (0.38%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

intestinal haemorrhage			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
intestinal obstruction			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	8 / 529 (1.51%)	11 / 528 (2.08%)	
occurrences causally related to treatment / all	1 / 8	0 / 11	
deaths causally related to treatment / all	0 / 2	0 / 2	
intestinal perforation			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	3 / 529 (0.57%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	2 / 2	0 / 0	
large intestinal haemorrhage			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	1 / 1	1 / 1	
large intestinal obstruction			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	3 / 529 (0.57%)	3 / 528 (0.57%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
large intestinal stenosis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	2 / 528 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
large intestine perforation			
alternative dictionary used: MedDRA 17.1			

subjects affected / exposed	4 / 529 (0.76%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	2 / 4	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
lower gastrointestinal haemorrhage			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	4 / 528 (0.76%)	
occurrences causally related to treatment / all	1 / 1	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
mechanical ileus			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
nausea			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	8 / 529 (1.51%)	6 / 528 (1.14%)	
occurrences causally related to treatment / all	4 / 8	6 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
oesophageal varices haemorrhage			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
oesophagitis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
proctalgia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

rectal haemorrhage			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	2 / 528 (0.38%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
rectal obstruction			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
rectal perforation			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
rectal ulcer			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
small intestinal haemorrhage			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
small intestinal obstruction			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	7 / 529 (1.32%)	5 / 528 (0.95%)	
occurrences causally related to treatment / all	0 / 7	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
small intestinal perforation			
alternative dictionary used: MedDRA 17.1			

subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
stomatitis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	3 / 528 (0.57%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
subileus			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
vomiting			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	13 / 529 (2.46%)	6 / 528 (1.14%)	
occurrences causally related to treatment / all	9 / 14	6 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
acute hepatic failure			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
bile duct obstruction			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	2 / 529 (0.38%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
bile duct stenosis			
alternative dictionary used: MedDRA 17.1			

subjects affected / exposed	1 / 529 (0.19%)	2 / 528 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
cholangitis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
cholangitis chronic			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
cholecystitis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	2 / 528 (0.38%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
cholelithiasis obstructive			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
cholestasis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hepatic cirrhosis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

hepatic failure			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hepatic function abnormal			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hepatorenal syndrome			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hepatotoxicity			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hyperbilirubinaemia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
jaundice			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
jaundice cholestatic			
alternative dictionary used: MedDRA 17.1			

subjects affected / exposed	1 / 529 (0.19%)	2 / 528 (0.38%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
liver disorder			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
portal hypertension			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
dermal cyst			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
skin ulcer			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	2 / 529 (0.38%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
acute prerenal failure			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
haematuria			
alternative dictionary used: MedDRA 17.1			

subjects affected / exposed	1 / 529 (0.19%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
hydronephrosis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	2 / 529 (0.38%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
nephrolithiasis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
nephrotic syndrome			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	3 / 529 (0.57%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	6 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
prerenal failure			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
renal failure			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
renal failure acute			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	3 / 529 (0.57%)	6 / 528 (1.14%)	
occurrences causally related to treatment / all	1 / 4	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	

urinary incontinence			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
urinary retention			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	2 / 529 (0.38%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
urinary tract obstruction			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
back pain			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	2 / 529 (0.38%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
musculoskeletal pain			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
neuropathic arthropathy			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
rheumatoid arthritis			
alternative dictionary used: MedDRA 17.1			

subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
abdominal infection			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
atypical pneumonia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
bacteraemia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	2 / 529 (0.38%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
biliary tract infection			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
bronchitis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
bronchopulmonary aspergillosis			
alternative dictionary used: MedDRA 17.1			

subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
campylobacter gastroenteritis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
cellulitis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
clostridium difficile colitis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	4 / 529 (0.76%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	4 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
cystitis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
device related infection			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
device related sepsis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

erysipelas			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
escherichia sepsis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
gastroenteritis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	2 / 528 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
herpes zoster			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
infection			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	2 / 529 (0.38%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
infective exacerbation of chronic obstructive airways disease			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
influenza			
alternative dictionary used: MedDRA 17.1			

subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
klebsiella infection			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
klebsiella sepsis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	2 / 528 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
localised infection			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
lung abscess			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
lung infection			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
mastoiditis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

neutropenic infection			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
oral candidiasis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pelvic abscess			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pelvic infection			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
perirectal abscess			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	2 / 528 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
peritonitis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	2 / 529 (0.38%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
peritonitis bacterial			
alternative dictionary used: MedDRA 17.1			

subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pneumonia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	7 / 529 (1.32%)	7 / 528 (1.33%)	
occurrences causally related to treatment / all	3 / 7	2 / 7	
deaths causally related to treatment / all	0 / 0	0 / 1	
pyelonephritis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
respiratory tract infection			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
salmonellosis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
sepsis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	5 / 529 (0.95%)	11 / 528 (2.08%)	
occurrences causally related to treatment / all	0 / 5	4 / 13	
deaths causally related to treatment / all	0 / 4	0 / 2	
septic shock			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	2 / 529 (0.38%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 2	0 / 0	

sinusitis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
upper respiratory tract infection			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
urinary tract infection			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	4 / 529 (0.76%)	5 / 528 (0.95%)	
occurrences causally related to treatment / all	1 / 4	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
wound infection			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
cachexia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
decreased appetite			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	7 / 529 (1.32%)	3 / 528 (0.57%)	
occurrences causally related to treatment / all	5 / 8	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
dehydration			
alternative dictionary used: MedDRA 17.1			

subjects affected / exposed	3 / 529 (0.57%)	6 / 528 (1.14%)	
occurrences causally related to treatment / all	2 / 4	2 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
hyperglycaemia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypoalbuminaemia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypokalaemia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	3 / 528 (0.57%)	
occurrences causally related to treatment / all	1 / 3	3 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
malnutrition			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 529 (0.19%)	0 / 528 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
tumour lysis syndrome			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 529 (0.00%)	1 / 528 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	FOLFIRI + Ramucirumab every 2 weeks	FOLFIRI + Placebo every 2 weeks	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	518 / 529 (97.92%)	510 / 528 (96.59%)	
Vascular disorders			
hypertension			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	147 / 529 (27.79%)	51 / 528 (9.66%)	
occurrences (all)	287	108	
General disorders and administration site conditions			
asthenia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	74 / 529 (13.99%)	62 / 528 (11.74%)	
occurrences (all)	228	168	
fatigue			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	254 / 529 (48.02%)	225 / 528 (42.61%)	
occurrences (all)	645	588	
malaise			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	41 / 529 (7.75%)	38 / 528 (7.20%)	
occurrences (all)	97	104	
mucosal inflammation			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	91 / 529 (17.20%)	52 / 528 (9.85%)	
occurrences (all)	218	92	
oedema peripheral			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	118 / 529 (22.31%)	50 / 528 (9.47%)	
occurrences (all)	148	59	
pyrexia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	85 / 529 (16.07%)	61 / 528 (11.55%)	
occurrences (all)	135	93	
Respiratory, thoracic and mediastinal disorders			

cough			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	69 / 529 (13.04%)	46 / 528 (8.71%)	
occurrences (all)	88	60	
dysphonia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	31 / 529 (5.86%)	5 / 528 (0.95%)	
occurrences (all)	32	6	
dyspnoea			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	56 / 529 (10.59%)	51 / 528 (9.66%)	
occurrences (all)	86	70	
epistaxis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	182 / 529 (34.40%)	80 / 528 (15.15%)	
occurrences (all)	254	99	
hiccups			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	30 / 529 (5.67%)	17 / 528 (3.22%)	
occurrences (all)	81	22	
Psychiatric disorders			
insomnia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	47 / 529 (8.88%)	54 / 528 (10.23%)	
occurrences (all)	51	84	
Investigations			
alanine aminotransferase increased			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	28 / 529 (5.29%)	19 / 528 (3.60%)	
occurrences (all)	59	59	
aspartate aminotransferase increased			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	34 / 529 (6.43%)	18 / 528 (3.41%)	
occurrences (all)	57	42	
blood alkaline phosphatase increased			

alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	36 / 529 (6.81%)	27 / 528 (5.11%)	
occurrences (all)	66	57	
neutrophil count decreased			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	137 / 529 (25.90%)	115 / 528 (21.78%)	
occurrences (all)	437	278	
platelet count decreased			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	80 / 529 (15.12%)	36 / 528 (6.82%)	
occurrences (all)	232	59	
weight decreased			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	76 / 529 (14.37%)	46 / 528 (8.71%)	
occurrences (all)	124	69	
white blood cell count decreased			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	49 / 529 (9.26%)	51 / 528 (9.66%)	
occurrences (all)	146	136	
Nervous system disorders			
dizziness			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	38 / 529 (7.18%)	33 / 528 (6.25%)	
occurrences (all)	46	51	
dysgeusia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	43 / 529 (8.13%)	39 / 528 (7.39%)	
occurrences (all)	57	57	
headache			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	80 / 529 (15.12%)	41 / 528 (7.77%)	
occurrences (all)	114	69	
peripheral sensory neuropathy			
alternative dictionary used: MedDRA 17.1			

subjects affected / exposed	33 / 529 (6.24%)	38 / 528 (7.20%)	
occurrences (all)	57	49	
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	93 / 529 (17.58%)	117 / 528 (22.16%)	
occurrences (all)	225	270	
neutropenia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	183 / 529 (34.59%)	131 / 528 (24.81%)	
occurrences (all)	510	259	
thrombocytopenia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	80 / 529 (15.12%)	42 / 528 (7.95%)	
occurrences (all)	177	82	
Gastrointestinal disorders			
abdominal distension			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	22 / 529 (4.16%)	27 / 528 (5.11%)	
occurrences (all)	26	29	
abdominal pain			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	124 / 529 (23.44%)	123 / 528 (23.30%)	
occurrences (all)	178	181	
constipation			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	157 / 529 (29.68%)	132 / 528 (25.00%)	
occurrences (all)	227	196	
diarrhoea			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	315 / 529 (59.55%)	271 / 528 (51.33%)	
occurrences (all)	881	798	
dyspepsia			
alternative dictionary used: MedDRA 17.1			

subjects affected / exposed	26 / 529 (4.91%)	27 / 528 (5.11%)	
occurrences (all)	28	32	
haemorrhoids			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	27 / 529 (5.10%)	6 / 528 (1.14%)	
occurrences (all)	33	7	
nausea			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	265 / 529 (50.09%)	274 / 528 (51.89%)	
occurrences (all)	650	715	
proctalgia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	27 / 529 (5.10%)	13 / 528 (2.46%)	
occurrences (all)	35	16	
stomatitis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	166 / 529 (31.38%)	113 / 528 (21.40%)	
occurrences (all)	380	235	
vomiting			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	151 / 529 (28.54%)	143 / 528 (27.08%)	
occurrences (all)	299	309	
Skin and subcutaneous tissue disorders			
alopecia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	156 / 529 (29.49%)	168 / 528 (31.82%)	
occurrences (all)	198	191	
dry skin			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	29 / 529 (5.48%)	23 / 528 (4.36%)	
occurrences (all)	35	25	
palmar-plantar erythrodysaesthesia syndrome			
alternative dictionary used: MedDRA 17.1			

subjects affected / exposed	69 / 529 (13.04%)	29 / 528 (5.49%)	
occurrences (all)	108	39	
rash			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	42 / 529 (7.94%)	36 / 528 (6.82%)	
occurrences (all)	47	45	
Renal and urinary disorders			
proteinuria			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	94 / 529 (17.77%)	30 / 528 (5.68%)	
occurrences (all)	227	40	
Musculoskeletal and connective tissue disorders			
arthralgia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	33 / 529 (6.24%)	22 / 528 (4.17%)	
occurrences (all)	38	26	
back pain			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	43 / 529 (8.13%)	48 / 528 (9.09%)	
occurrences (all)	54	128	
pain in extremity			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	36 / 529 (6.81%)	19 / 528 (3.60%)	
occurrences (all)	58	25	
Infections and infestations			
upper respiratory tract infection			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	36 / 529 (6.81%)	22 / 528 (4.17%)	
occurrences (all)	44	25	
urinary tract infection			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	34 / 529 (6.43%)	21 / 528 (3.98%)	
occurrences (all)	43	35	
Metabolism and nutrition disorders			

decreased appetite			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	203 / 529 (38.37%)	149 / 528 (28.22%)	
occurrences (all)	382	359	
dehydration			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	32 / 529 (6.05%)	26 / 528 (4.92%)	
occurrences (all)	46	32	
hypoalbuminaemia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	35 / 529 (6.62%)	13 / 528 (2.46%)	
occurrences (all)	59	20	
hypokalaemia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	39 / 529 (7.37%)	38 / 528 (7.20%)	
occurrences (all)	65	72	

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