



Clinical trial results:

A Randomised, Double-blind, Phase III Study to Compare the Efficacy and

Safety of Cediranib (AZD2171) when added to 5-fluorouracil, Leucovorin and Oxaliplatin (FOLFOX) or Capecitabine and Oxaliplatin (XELOX) with the Efficacy and Safety of Placebo when added to FOLFOX or XELOX in Patients with Previously Untreated Metastatic Colorectal Cancer

Summary

EudraCT number	2006-001194-14
Trial protocol	DE CZ HU GB
Global end of trial date	17 August 2016

Results information

Result version number	v1 (current)
This version publication date	02 September 2017
First version publication date	02 September 2017

Trial information

Trial identification

Sponsor protocol code	D8480C00051
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00399035
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	132 Hills Road, Cambridge, United Kingdom, CB2 1PG
Public contact	Tsveta Milenkova, AstraZeneca, ClinicalTrialTransparency@astrazeneca.com
Scientific contact	Tsveta Milenkova, AstraZeneca, ClinicalTrialTransparency@astrazeneca.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 March 2010
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 March 2010
Global end of trial reached?	Yes
Global end of trial date	17 August 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to determine the efficacy of cediranib when added to FOLFOX or XELOX compared to the efficacy of FOLFOX or XELOX alone in patients with previously untreated metastatic CRC, by assessment of the co-primary endpoints of PFS and OS.

Protection of trial subjects:

If toxicity is encountered, the dose of cediranib may be reduced or treatment with cediranib stopped (for a maximum of 14 days) until resolution of symptoms. At the discretion of the investigator, study treatment may be restarted. Within a patient, the dose of cediranib can be reduced up to two times; for those patients receiving 20 mg cediranib there will only be one active dose reduction to 15 mg.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 November 2006
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 54
Country: Number of subjects enrolled	Australia: 68
Country: Number of subjects enrolled	Brazil: 204
Country: Number of subjects enrolled	Bulgaria: 147
Country: Number of subjects enrolled	China: 192
Country: Number of subjects enrolled	Czech Republic: 108
Country: Number of subjects enrolled	Germany: 40
Country: Number of subjects enrolled	Hungary: 118
Country: Number of subjects enrolled	India: 29
Country: Number of subjects enrolled	Korea, Republic of: 47
Country: Number of subjects enrolled	Philippines: 48
Country: Number of subjects enrolled	Poland: 97
Country: Number of subjects enrolled	Switzerland: 24
Country: Number of subjects enrolled	Thailand: 21
Country: Number of subjects enrolled	United Kingdom: 57
Worldwide total number of subjects	1254
EEA total number of subjects	567

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)	849
From 65 to 84 years	405
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Randomised=full analysis set: Cediranib 20mg=502, Cediranib 30mg=216, Placebo=358; Safety set: Cediranib 20mg=500, Cediranib 30mg=214, Placebo=358. Primary analysis and results reported for Cediranib 20mg vs placebo.

Pre-assignment

Screening details:

Cediranib 30mg discontinued after Phase II, Cediranib 20mg chosen for comparing with Placebo. 1254 patients enrolled to the study, 1076 received study treatment; 2 patients didn't receive cediranib/placebo for Cediranib 20 mg, and 2 patients didn't receive cediranib/placebo for Cediranib 30 mg.

The 4 patients that didn't receive drug are included.

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cediranib 20 mg/day

Arm description:

[Cediranib 20mg/day+FOLFOX/XELOX]. 2 FOLFOX regimens were chosen: FOLFOX4 or mFOLFOX6 (repeated every 2 weeks). FOLFOX4: oxaliplatin 85mg/m² dosed by iv infusion over 2h on Day1; leucovorin 200mg/m² (or equivalent folinic acid preparation) by iv infusion over 2h on Day1 and Day2; 5-FU 400mg/m² iv bolus immediately after completion of the oxaliplatin/leucovorin infusion on Day1 and Day2; 5-FU 600 mg/m² immediately after the 5-FU bolus dosed by continuous iv infusion over 22h on Day1 and Day2. mFOLFOX6: oxaliplatin 85mg/m² dosed by iv infusion over 2h on Day1; leucovorin 400mg/m² (or equivalent folinic acid preparation) dosed iv over 2h on Day1; 5-FU 400mg/m² iv bolus immediately after completion of the oxaliplatin/leucovorin infusion on Day1, followed immediately by 5-FU 2400mg/m² dosed by continuous iv infusion over 46h. XELOX: The XELOX regimen was to be repeated every 3 weeks: oxaliplatin 130mg/m² dosed by iv infusion over 2h on Day1; capecitabine 1000mg/m² orally twice daily on Days1 to 14.

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

Dosage and administration details:

20 mg orally once daily

Arm title	Cediranib 30 mg/day
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Arm description:

[Cediranib 30mg/day+FOLFOX/XELOX]. 2 FOLFOX regimens were chosen: FOLFOX4 or mFOLFOX6 (repeated every 2 weeks). FOLFOX4: oxaliplatin 85mg/m² dosed by iv infusion over 2h on Day1; leucovorin 200mg/m² (or equivalent folinic acid preparation) by iv infusion over 2h on Day1 and Day2; 5-FU 400mg/m² iv bolus immediately after completion of the oxaliplatin/leucovorin infusion on Day1 and Day2; 5-FU 600 mg/m² immediately after the 5-FU bolus dosed by continuous iv infusion over 22h on Day1 and Day2. mFOLFOX6: oxaliplatin 85mg/m² dosed by iv infusion over 2h on Day1; leucovorin 400mg/m² (or equivalent folinic acid preparation) dosed iv over 2h on Day1; 5-FU 400mg/m² iv bolus immediately after completion of the oxaliplatin/leucovorin infusion on Day1, followed immediately by 5-FU 2400mg/m² dosed by continuous iv infusion over 46h. XELOX: The XELOX regimen was to be repeated every 3 weeks: oxaliplatin 130mg/m² dosed by iv infusion over 2h on Day1; capecitabine 1000mg/m² orally twice daily on Days1 to 14.

Arm type	Experimental
Investigational medicinal product name	cediranib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details:	
30mg orally once daily	
Arm title	Placebo

Arm description:

[Placebo +FOLFOX/XELOX].2 FOLFOX regimens were chosen:FOLFOX4 or mFOLFOX6(repeated every 2 weeks.FOLFOX4:oxaliplatin 85mg/m2 dosed by iv infusion over 2h on Day1;leucovorin 200mg/m2(or equivalent folinic acid preparation) by iv infusion over 2h on Day1 and Day2;5-FU 400mg/m2 iv bolus immediately after completion of the oxaliplatin/leucovorin infusion on Day1 and Day2;5-FU 600 mg/m2 immediately after the 5-FU bolus dosed by continuous iv infusion over 22h on Day1 and Day2.mFOLFOX6:oxaliplatin 85mg/m2 dosed by iv infusion over 2h on Day1;leucovorin 400mg/m2(or equivalent folinic acid preparation)dosed iv over 2h on Day1;5-FU 400mg/m2 iv bolus immediately after completion of the oxaliplatin/leucovorin infusion on Day1, followed immediately by 5-FU 2400mg/m2 dosed by continuous iv infusion over 46h.XELOX:The XELOX regimen was to be repeated every 3 weeks:oxaliplatin 130mg/m2 dosed by iv infusion over 2h on Day1;capecitabine 1000mg/m2 orally twice daily on Days1 to 14.

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

Dosage and administration details:

20mg orally once daily

Number of subjects in period 1^[1]	Cediranib 20 mg/day	Cediranib 30 mg/day	Placebo
Started	502	216	358
Completed	189	58	106
Not completed	313	158	252
Adverse event, serious fatal	289	141	234
Consent withdrawn by subject	19	15	12
Severe non-compliance with protocol	2	1	-
Incorrect enrolment/eligib not fulfilled	1	-	1
Lost to follow-up	2	1	5

Notes:

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

Justification: 1254 patients enrolled to the study described in worldwide recruitment section, 1076 randomised to study treatment and described in baseline, efficacy and safety sections.

Baseline characteristics

Reporting groups

Reporting group title	Cediranib 20 mg/day
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Reporting group description:

[Cediranib 20mg/day+FOLFOX/XELOX].2 FOLFOX regimens were chosen:FOLFOX4 or mFOLFOX6(repeated every 2 weeks.FOLFOX4:oxaliplatin 85mg/m2 dosed by iv infusion over 2h on Day1;leucovorin 200mg/m2(or equivalent folinic acid preparation) by iv infusion over 2h on Day1 and Day2;5-FU 400mg/m2 iv bolus immediately after completion of the oxaliplatin/leucovorin infusion on Day1 and Day2;5-FU 600 mg/m2 immediately after the 5-FU bolus dosed by continuous iv infusion over 22h on Day1 and Day2.mFOLFOX6:oxaliplatin 85mg/m2 dosed by iv infusion over 2h on Day1;leucovorin 400mg/m2(or equivalent folinic acid preparation)dosed iv over 2h on Day1;5-FU 400mg/m2 iv bolus immediately after completion of the oxaliplatin/leucovorin infusion on Day1, followed immediately by 5-FU 2400mg/m2 dosed by continuous iv infusion over 46h.XELOX:The XELOX regimen was to be repeated every 3 weeks:oxaliplatin 130mg/m2 dosed by iv infusion over 2h on Day1;capecitabine 1000mg/m2 orally twice daily on Days1 to 14.

Reporting group title	Cediranib 30 mg/day
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Reporting group description:

[Cediranib 30mg/day+FOLFOX/XELOX].2 FOLFOX regimens were chosen:FOLFOX4 or mFOLFOX6(repeated every 2 weeks.FOLFOX4:oxaliplatin 85mg/m2 dosed by iv infusion over 2h on Day1;leucovorin 200mg/m2(or equivalent folinic acid preparation) by iv infusion over 2h on Day1 and Day2;5-FU 400mg/m2 iv bolus immediately after completion of the oxaliplatin/leucovorin infusion on Day1 and Day2;5-FU 600 mg/m2 immediately after the 5-FU bolus dosed by continuous iv infusion over 22h on Day1 and Day2.mFOLFOX6:oxaliplatin 85mg/m2 dosed by iv infusion over 2h on Day1;leucovorin 400mg/m2(or equivalent folinic acid preparation)dosed iv over 2h on Day1;5-FU 400mg/m2 iv bolus immediately after completion of the oxaliplatin/leucovorin infusion on Day1, followed immediately by 5-FU 2400mg/m2 dosed by continuous iv infusion over 46h.XELOX:The XELOX regimen was to be repeated every 3 weeks:oxaliplatin 130mg/m2 dosed by iv infusion over 2h on Day1;capecitabine 1000mg/m2 orally twice daily on Days1 to 14.

Reporting group title	Placebo
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Reporting group description:

[Placebo +FOLFOX/XELOX].2 FOLFOX regimens were chosen:FOLFOX4 or mFOLFOX6(repeated every 2 weeks.FOLFOX4:oxaliplatin 85mg/m2 dosed by iv infusion over 2h on Day1;leucovorin 200mg/m2(or equivalent folinic acid preparation) by iv infusion over 2h on Day1 and Day2;5-FU 400mg/m2 iv bolus immediately after completion of the oxaliplatin/leucovorin infusion on Day1 and Day2;5-FU 600 mg/m2 immediately after the 5-FU bolus dosed by continuous iv infusion over 22h on Day1 and Day2.mFOLFOX6:oxaliplatin 85mg/m2 dosed by iv infusion over 2h on Day1;leucovorin 400mg/m2(or equivalent folinic acid preparation)dosed iv over 2h on Day1;5-FU 400mg/m2 iv bolus immediately after completion of the oxaliplatin/leucovorin infusion on Day1, followed immediately by 5-FU 2400mg/m2 dosed by continuous iv infusion over 46h.XELOX:The XELOX regimen was to be repeated every 3 weeks:oxaliplatin 130mg/m2 dosed by iv infusion over 2h on Day1;capecitabine 1000mg/m2 orally twice daily on Days1 to 14.

Reporting group values	Cediranib 20 mg/day	Cediranib 30 mg/day	Placebo
Number of subjects	502	216	358
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	343	148	245
From 65-84 years	159	68	113

85 years and over	0	0	0
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Age Continuous Units: years arithmetic mean standard deviation	57.8 ± 11.14	59.4 ± 10.69	57.2 ± 11.63
Gender, Male/Female			
Gender at informed consent			
Units: participants			
Female	203	93	146
Male	299	123	212

Reporting group values	Total		
Number of subjects	1076		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	736		
From 65-84 years	340		
85 years and over	0		
Age Continuous Units: years arithmetic mean standard deviation	-		
Gender, Male/Female			
Gender at informed consent			
Units: participants			
Female	442		
Male	634		

End points

End points reporting groups

Reporting group title	Cediranib 20 mg/day
Reporting group description:	
[Cediranib 20mg/day+FOLFOX/XELOX].2 FOLFOX regimens were chosen:FOLFOX4 or mFOLFOX6(repeated every 2 weeks.FOLFOX4:oxaliplatin 85mg/m2 dosed by iv infusion over 2h on Day1;leucovorin 200mg/m2(or equivalent folinic acid preparation) by iv infusion over 2h on Day1 and Day2;5-FU 400mg/m2 iv bolus immediately after completion of the oxaliplatin/leucovorin infusion on Day1 and Day2;5-FU 600 mg/m2 immediately after the 5-FU bolus dosed by continuous iv infusion over 22h on Day1 and Day2.mFOLFOX6:oxaliplatin 85mg/m2 dosed by iv infusion over 2h on Day1;leucovorin 400mg/m2(or equivalent folinic acid preparation)dosed iv over 2h on Day1;5-FU 400mg/m2 iv bolus immediately after completion of the oxaliplatin/leucovorin infusion on Day1,followed immediately by 5-FU 2400mg/m2 dosed by continuous iv infusion over 46h.XELOX:The XELOX regimen was to be repeated every 3 weeks:oxaliplatin 130mg/m2 dosed by iv infusion over 2h on Day1;capecitabine 1000mg/m2 orally twice daily on Days1 to 14.	
Reporting group title	Cediranib 30 mg/day
Reporting group description:	
[Cediranib 30mg/day+FOLFOX/XELOX].2 FOLFOX regimens were chosen:FOLFOX4 or mFOLFOX6(repeated every 2 weeks.FOLFOX4:oxaliplatin 85mg/m2 dosed by iv infusion over 2h on Day1;leucovorin 200mg/m2(or equivalent folinic acid preparation) by iv infusion over 2h on Day1 and Day2;5-FU 400mg/m2 iv bolus immediately after completion of the oxaliplatin/leucovorin infusion on Day1 and Day2;5-FU 600 mg/m2 immediately after the 5-FU bolus dosed by continuous iv infusion over 22h on Day1 and Day2.mFOLFOX6:oxaliplatin 85mg/m2 dosed by iv infusion over 2h on Day1;leucovorin 400mg/m2(or equivalent folinic acid preparation)dosed iv over 2h on Day1;5-FU 400mg/m2 iv bolus immediately after completion of the oxaliplatin/leucovorin infusion on Day1,followed immediately by 5-FU 2400mg/m2 dosed by continuous iv infusion over 46h.XELOX:The XELOX regimen was to be repeated every 3 weeks:oxaliplatin 130mg/m2 dosed by iv infusion over 2h on Day1;capecitabine 1000mg/m2 orally twice daily on Days1 to 14.	
Reporting group title	Placebo
Reporting group description:	
[Placebo +FOLFOX/XELOX].2 FOLFOX regimens were chosen:FOLFOX4 or mFOLFOX6(repeated every 2 weeks.FOLFOX4:oxaliplatin 85mg/m2 dosed by iv infusion over 2h on Day1;leucovorin 200mg/m2(or equivalent folinic acid preparation) by iv infusion over 2h on Day1 and Day2;5-FU 400mg/m2 iv bolus immediately after completion of the oxaliplatin/leucovorin infusion on Day1 and Day2;5-FU 600 mg/m2 immediately after the 5-FU bolus dosed by continuous iv infusion over 22h on Day1 and Day2.mFOLFOX6:oxaliplatin 85mg/m2 dosed by iv infusion over 2h on Day1;leucovorin 400mg/m2(or equivalent folinic acid preparation)dosed iv over 2h on Day1;5-FU 400mg/m2 iv bolus immediately after completion of the oxaliplatin/leucovorin infusion on Day1,followed immediately by 5-FU 2400mg/m2 dosed by continuous iv infusion over 46h.XELOX:The XELOX regimen was to be repeated every 3 weeks:oxaliplatin 130mg/m2 dosed by iv infusion over 2h on Day1;capecitabine 1000mg/m2 orally twice daily on Days1 to 14.	

Primary: Progression-free survival

End point title	Progression-free survival ^[1]
End point description:	
RECIST criteria defined as follows: Target lesions Complete Response (CR) Disappearance of all target lesions Partial Response (PR) At least a 30% decrease in the sum of LD of target lesions taking as reference the baseline sum LD.Progressive Disease (PD) At least a 20% increase in the sum of LD of target lesions taking as references the smallest sum LD recorded (either at baseline or at previous assessment since treatment began).Stable Disease (SD) Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. Non-target lesions Complete Response (CR) Disappearance of all non-target lesions Non-Complete Response (non-CR/Non- Progression [non-PD]) Persistence of one or more non-target lesion or/and maintenance of tumour marker level above the normal limits. Progression (PD) Unequivocal progression of existing nontarget lesions.	
End point type	Primary
End point timeframe:	
RECIST assessed at baseline every 6 weeks through to week 24 and 12 week thereafter through to progression or data cut off date of 21/03/10 whichever was earliest.	

Notes:

[1] - 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: The endpoint presented is observed during follow-up, but not observable at baseline, nor is a "change from baseline" calculation appropriate for this endpoint.

End point values	Cediranib 20 mg/day	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	502	358		
Units: Months				
median (inter-quartile range (Q1-Q3))	8.6 (5.5 to 12.1)	8.2 (4.1 to 11.1)		

Statistical analyses

Statistical analysis title	Cox PH model
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Statistical analysis description:

The effect of treatment was be estimated by the adjusted HR together with its 95% CI, which was calculated from a Cox PH model fitted with the following covariates: performance status, the chemotherapy received, a twolevel baseline liver function covariate and study phase covariate. The model will be fitted using SAS's PROC PHREG using the Breslow method for ties.

Comparison groups	Cediranib 20 mg/day v Placebo
Number of subjects included in analysis	860
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0121 [2]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	Other: 0.95 %
sides	2-sided
lower limit	0.73
upper limit	0.98

Notes:

[2] - Statistically significant

Statistical analysis title	Alternative censoring mechanism (FAS, ITT)
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Statistical analysis description:

The first sensitivity analysis considered all progression events regardless of whether they occurred after 2 or more consecutive non-evaluable visits, or after patients had received another cancer therapy prior to progression. The results of this analysis were consistent with the primary analysis, indicating that the choice of censoring mechanism in the primary analysis did not influence the overall results.

Comparison groups	Cediranib 20 mg/day v Placebo
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Number of subjects included in analysis	860
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0183 ^[3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	Other: 0.95 %
sides	2-sided
lower limit	0.73
upper limit	0.97

Notes:

[3] - P-value estimated from log-rank test stratified by same factors used in Cox Proportional Hazards model

Statistical analysis title	Interval-censored approach (FAS, ITT)
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Statistical analysis description:

The interval-censored analysis, which compared the proportion of patients progressing during discrete time intervals post-randomisation, was also consistent with the primary analysis, indicating that there was no bias due to any differences in the frequency of assessments between treatment arms

Comparison groups	Cediranib 20 mg/day v Placebo
Number of subjects included in analysis	860
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0279
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.85
Confidence interval	
level	Other: 0.95 %
sides	2-sided
lower limit	0.73
upper limit	0.98

Statistical analysis title	Central review (FAS, ITT)
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Statistical analysis description:

Another post-hoc analysis was done to assess the impact of primary tumour location (colon or rectal) on the treatment effect for PFS, as a slight imbalance was observed in primary tumour location: 57.4% of patients on the cediranib arm versus 64.8% on the placebo arm had primary colon cancer. The HR for site of primary tumour was not significant, indicating that it was not a prognostic factor (HR=0.98; 95% CI 0.84, 1.14) and when included in the model did not affect the treatment effect HR.

Comparison groups	Cediranib 20 mg/day v Placebo
Number of subjects included in analysis	860
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0307 ^[4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.86

Confidence interval	
level	Other: 0.95 %
sides	2-sided
lower limit	0.73
upper limit	1.02

Notes:

[4] - P-value estimated from log-rank test stratified by same factors used in Cox Proportional Hazards model

Primary: Overall survival

End point title	Overall survival ^[5]
End point description:	
Number of months from randomisation to the date of death from any cause	
End point type	Primary
End point timeframe:	
Baseline through to date of death upto and including data cut off date of 21/03/10	

Notes:

[5] - 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: The endpoint presented is observed during follow-up, but not observable at baseline, nor is a "change from baseline" calculation appropriate for this endpoint.

End point values	Cediranib 20 mg/day	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	502	358		
Units: Months				
median (inter-quartile range (Q1-Q3))	19.7 (11 to 36.1)	18.9 (11 to 28.9)		

Statistical analyses

Statistical analysis title	OS analysis
Statistical analysis description:	
At the time of the data-cut off, a total of 523 patients (60.8% of total study population) had died, indicating a mature OS data set. Median follow-up was 22 months (21.8 months on cediranib 20 mg, and 23.1 months on placebo); therefore, most censored patients were represented towards the latter part of the Kaplan-Meier curve. Once the actual number of events became known it was possible to calculate the exact significance level. Accounting for Type 1 error, p <0.0491 was significant for OS.	
Comparison groups	Cediranib 20 mg/day v Placebo
Number of subjects included in analysis	860
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.5707 ^[6]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.94
Confidence interval	
level	Other: 0.95 %
sides	2-sided
lower limit	0.79
upper limit	1.12

Notes:

[6] - P-value estimated from a Log-Rank test stratifying for performance status (0 or 1), chemotherapy received, baseline liver function, and study phase (randomised before or after dropping of the 30 mg arm).

Secondary: Overall response rate

End point title	Overall response rate ^[7]
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End point description:

Objective tumour response(defined as a confirmed response of CR or PR).The definition for a confirmed response was met when an initial RECIST response of PR/CR was confirmed at the next scheduled visit as a PR/CR according to an evaluable assessment.Intervening assessments of non-evaluable or stable disease were allowable as long as the initial RECIST response was confirmed.RECIST criteria defined as follows: Target lesions Complete Response(CR)Disappearance of all target lesions Partial Response (PR).At least a 30% decrease in the sum of LD of target lesions taking as reference the baseline sum LD. Progressive Disease (PD) At least a 20% increase in the sum of LD of target lesions taking as references the smallest sum LD recorded (either at baseline or at previous assessment since treatment began).Stable Disease (SD) Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.Non-target lesions Complete Response (CR) Disappearance of all non-target lesi

End point type	Secondary
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End point timeframe:

Baseline through to date of death upto and including data cut off date of 21/03/10

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: The endpoint presented is observed during follow-up, but not observable at baseline, nor is a "change from baseline" calculation appropriate for this endpoint.

End point values	Cediranib 20 mg/day	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	502	358		
Units: Participants	254	178		

Statistical analyses

No statistical analyses for this end point

Secondary: Best percentage change in tumour size

End point title	Best percentage change in tumour size ^[8]
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End point description:

Maximum percentage reduction or minimum percentage increase in tumour size where size is the sum of the longest diameters of the target lesions

End point type	Secondary
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End point timeframe:

Baseline through to date of death upto and including data cut off date of 21/03/10

Notes:

[8] - 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: The endpoint presented is observed during follow-up, but not observable at baseline, nor is a "change from baseline" calculation appropriate for this endpoint.

End point values	Cediranib 20 mg/day	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	474	339		
Units: Percentage [change in tumour size (mm)]				
arithmetic mean (standard deviation)	-42.49 (± 28.139)	-40.61 (± 31.992)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response

End point title	Duration of response ^[9]
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End point description:

Based on RECIST measurements taken throughout the study and best objective tumour response at the defined analysis cut-off point. Measured from the time the criteria for CR/PR are first met (whichever is recorded first) until the patient progresses or dies.

End point type	Secondary
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End point timeframe:

Treatment period from initial response up until data cut-off date of 21/03/10

Notes:

[9] - 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: The endpoint presented is observed during follow-up, but not observable at baseline, nor is a "change from baseline" calculation appropriate for this endpoint.

End point values	Cediranib 20 mg/day	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	254	178		
Units: Months				
median (inter-quartile range (Q1-Q3))	8.5 (5.9 to 12.7)	6.9 (4.8 to 11)		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of resection of liver metastases

End point title	Rate of resection of liver metastases ^[10]
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End point description:

Number of patients undergoing liver resection, based on patients with liver disease at baseline

End point type	Secondary
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End point timeframe:

Post-randomisation until end of study

Notes:

[10] - 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: The endpoint presented is observed during follow-up, but not observable at baseline, nor is a "change from baseline" calculation appropriate for this endpoint.

End point values	Cediranib 20 mg/day	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	387	271		
Units: Participants	21	17		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to wound healing complications

End point title	Time to wound healing complications ^[11]
End point description:	
Number of days from post-randomisation surgery until wound healing complications	
End point type	Secondary
End point timeframe:	
Post-randomisation until end of study	

Notes:

[11] - 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: The endpoint presented is observed during follow-up, but not observable at baseline, nor is a "change from baseline" calculation appropriate for this endpoint.

End point values	Cediranib 20 mg/day	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	79		
Units: Days				
median (full range (min-max))	18 (1 to 93)	18 (0 to 114)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug until last study visit

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17
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Reporting groups

Reporting group title	Placebo
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Reporting group description:

Placebo

Reporting group title	cediranib 30 mg
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Reporting group description:

cediranib 30 mg

Reporting group title	cediranib 20 mg
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Reporting group description:

cediranib 20 mg

Serious adverse events	Placebo	cediranib 30 mg	cediranib 20 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	105 / 358 (29.33%)	94 / 214 (43.93%)	204 / 500 (40.80%)
number of deaths (all causes)	234	140	289
number of deaths resulting from adverse events	5	6	5
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
BASAL CELL CARCINOMA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	1 / 214 (0.47%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BENIGN NEOPLASM OF SPINAL CORD			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PENIS CARCINOMA			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RENAL CANCER			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SQUAMOUS CELL CARCINOMA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	1 / 214 (0.47%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
AORTIC THROMBOSIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	1 / 214 (0.47%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEEP VEIN THROMBOSIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 358 (0.28%)	2 / 214 (0.93%)	3 / 500 (0.60%)
occurrences causally related to treatment / all	0 / 1	1 / 2	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FEMORAL ARTERY OCCLUSION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERTENSION			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	2 / 358 (0.56%)	8 / 214 (3.74%)	6 / 500 (1.20%)
occurrences causally related to treatment / all	2 / 2	7 / 8	7 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERTENSIVE CRISIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	1 / 214 (0.47%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ORTHOSTATIC HYPOTENSION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 358 (0.28%)	1 / 214 (0.47%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERIPHERAL EMBOLISM			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERIPHERAL ISCHAEMIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	1 / 214 (0.47%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PHLEBITIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
THROMBOSIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	1 / 214 (0.47%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

<p>VENA CAVA THROMBOSIS</p> <p>alternative dictionary used: MedDRA 17</p> <p>subjects affected / exposed</p> <p>occurrences causally related to treatment / all</p> <p>deaths causally related to treatment / all</p>	<p>0 / 358 (0.00%)</p> <p>0 / 0</p> <p>0 / 0</p>	<p>0 / 214 (0.00%)</p> <p>0 / 0</p> <p>0 / 0</p>	<p>1 / 500 (0.20%)</p> <p>1 / 1</p> <p>0 / 0</p>
<p>General disorders and administration site conditions</p> <p>ASTHENIA</p> <p>alternative dictionary used: MedDRA 17</p> <p>subjects affected / exposed</p> <p>occurrences causally related to treatment / all</p> <p>deaths causally related to treatment / all</p>	<p>3 / 358 (0.84%)</p> <p>1 / 3</p> <p>0 / 0</p>	<p>1 / 214 (0.47%)</p> <p>1 / 1</p> <p>0 / 0</p>	<p>1 / 500 (0.20%)</p> <p>1 / 1</p> <p>0 / 0</p>
<p>DEATH</p> <p>alternative dictionary used: MedDRA 17</p> <p>subjects affected / exposed</p> <p>occurrences causally related to treatment / all</p> <p>deaths causally related to treatment / all</p>	<p>1 / 358 (0.28%)</p> <p>1 / 1</p> <p>1 / 1</p>	<p>2 / 214 (0.93%)</p> <p>0 / 2</p> <p>0 / 2</p>	<p>1 / 500 (0.20%)</p> <p>0 / 1</p> <p>0 / 1</p>
<p>FATIGUE</p> <p>alternative dictionary used: MedDRA 17</p> <p>subjects affected / exposed</p> <p>occurrences causally related to treatment / all</p> <p>deaths causally related to treatment / all</p>	<p>0 / 358 (0.00%)</p> <p>0 / 0</p> <p>0 / 0</p>	<p>2 / 214 (0.93%)</p> <p>2 / 2</p> <p>0 / 0</p>	<p>3 / 500 (0.60%)</p> <p>1 / 3</p> <p>0 / 0</p>
<p>GENERAL PHYSICAL HEALTH DETERIORATION</p> <p>alternative dictionary used: MedDRA 17</p> <p>subjects affected / exposed</p> <p>occurrences causally related to treatment / all</p> <p>deaths causally related to treatment / all</p>	<p>0 / 358 (0.00%)</p> <p>0 / 0</p> <p>0 / 0</p>	<p>1 / 214 (0.47%)</p> <p>1 / 1</p> <p>0 / 0</p>	<p>1 / 500 (0.20%)</p> <p>1 / 1</p> <p>0 / 0</p>
<p>INFUSION SITE IRRITATION</p> <p>alternative dictionary used: MedDRA 17</p> <p>subjects affected / exposed</p> <p>occurrences causally related to treatment / all</p> <p>deaths causally related to treatment / all</p>	<p>0 / 358 (0.00%)</p> <p>0 / 0</p> <p>0 / 0</p>	<p>1 / 214 (0.47%)</p> <p>1 / 1</p> <p>0 / 0</p>	<p>0 / 500 (0.00%)</p> <p>0 / 0</p> <p>0 / 0</p>
<p>MULTI-ORGAN FAILURE</p> <p>alternative dictionary used:</p>			

MedDRA 17			
subjects affected / exposed	1 / 358 (0.28%)	0 / 214 (0.00%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
PERFORMANCE STATUS DECREASED			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	1 / 214 (0.47%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYREXIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	4 / 358 (1.12%)	2 / 214 (0.93%)	5 / 500 (1.00%)
occurrences causally related to treatment / all	2 / 4	2 / 3	4 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUDDEN DEATH			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 358 (0.28%)	0 / 214 (0.00%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Immune system disorders			
ANAPHYLACTIC REACTION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	3 / 358 (0.84%)	0 / 214 (0.00%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DRUG HYPERSENSITIVITY			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	2 / 358 (0.56%)	1 / 214 (0.47%)	3 / 500 (0.60%)
occurrences causally related to treatment / all	1 / 2	1 / 1	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FOOD ALLERGY			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	0 / 358 (0.00%)	1 / 214 (0.47%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERSENSITIVITY			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	1 / 214 (0.47%)	2 / 500 (0.40%)
occurrences causally related to treatment / all	0 / 0	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
FEMALE GENITAL TRACT FISTULA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 358 (0.28%)	0 / 214 (0.00%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VAGINAL HAEMORRHAGE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	3 / 500 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
ASTHMA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DYSAESTHESIA PHARYNX			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 358 (0.28%)	0 / 214 (0.00%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DYSPNOEA			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	1 / 358 (0.28%)	1 / 214 (0.47%)	4 / 500 (0.80%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DYSпноEA EXERTIONAL			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	1 / 214 (0.47%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
EPISTAXIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	1 / 214 (0.47%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMOPTYSIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	1 / 214 (0.47%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HICCUPS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERVENTILATION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LARYNGOSPASM			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

LUNG INFILTRATION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PLEURAL EFFUSION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	2 / 358 (0.56%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONITIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMOTHORAX			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	1 / 214 (0.47%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PULMONARY ARTERY THROMBOSIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	1 / 214 (0.47%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PULMONARY EMBOLISM			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	4 / 358 (1.12%)	4 / 214 (1.87%)	10 / 500 (2.00%)
occurrences causally related to treatment / all	3 / 4	2 / 4	9 / 10
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
RESPIRATORY FAILURE			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	0 / 358 (0.00%)	1 / 214 (0.47%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Psychiatric disorders			
CONFUSIONAL STATE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 358 (0.28%)	1 / 214 (0.47%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERSONALITY CHANGE DUE TO A GENERAL MEDICAL CONDITION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUICIDE ATTEMPT			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 358 (0.28%)	0 / 214 (0.00%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
BILIRUBIN CONJUGATED INCREASED			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INTERNATIONAL NORMALISED RATIO INCREASED			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LIVER FUNCTION TEST ABNORMAL			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PLATELET COUNT DECREASED			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 358 (0.28%)	1 / 214 (0.47%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
COMMUNUTED FRACTURE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 358 (0.28%)	0 / 214 (0.00%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FEMUR FRACTURE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROINTESTINAL STOMA COMPLICATION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 358 (0.28%)	0 / 214 (0.00%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OVERDOSE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 358 (0.28%)	0 / 214 (0.00%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERONEAL NERVE INJURY			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	1 / 358 (0.28%)	0 / 214 (0.00%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
POST PROCEDURAL COMPLICATION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
POST PROCEDURAL HAEMORRHAGE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	4 / 358 (1.12%)	2 / 214 (0.93%)	2 / 500 (0.40%)
occurrences causally related to treatment / all	3 / 4	2 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
POSTOPERATIVE HERNIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
POSTOPERATIVE WOUND COMPLICATION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 358 (0.28%)	0 / 214 (0.00%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SPINAL FRACTURE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
STENT OCCLUSION			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	1 / 358 (0.28%)	0 / 214 (0.00%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUBDURAL HAEMATOMA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
UPPER LIMB FRACTURE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URETERIC INJURY			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
WOUND COMPLICATION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
WOUND DEHISCENCE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	1 / 214 (0.47%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
ACUTE LEFT VENTRICULAR FAILURE			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	1 / 358 (0.28%)	0 / 214 (0.00%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
ANGINA PECTORIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 358 (0.28%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ATRIAL FIBRILLATION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	3 / 358 (0.84%)	3 / 214 (1.40%)	2 / 500 (0.40%)
occurrences causally related to treatment / all	0 / 3	2 / 3	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BRADYCARDIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CARDIAC ARREST			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
CARDIAC FAILURE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	2 / 214 (0.93%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 2	0 / 0
CARDIOPULMONARY FAILURE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	1 / 214 (0.47%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

CORONARY ARTERY DISEASE alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 358 (0.00%) 0 / 0 0 / 0	0 / 214 (0.00%) 0 / 0 0 / 0	1 / 500 (0.20%) 1 / 1 0 / 0
MYOCARDIAL INFARCTION alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 358 (0.00%) 0 / 0 0 / 0	3 / 214 (1.40%) 1 / 3 0 / 1	1 / 500 (0.20%) 0 / 1 0 / 1
MYOCARDIAL ISCHAEMIA alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 358 (0.28%) 1 / 1 0 / 0	0 / 214 (0.00%) 0 / 0 0 / 0	2 / 500 (0.40%) 1 / 2 0 / 0
TACHYCARDIA alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 358 (0.28%) 0 / 1 0 / 0	0 / 214 (0.00%) 0 / 0 0 / 0	0 / 500 (0.00%) 0 / 0 0 / 0
VENTRICULAR ARRHYTHMIA alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 358 (0.00%) 0 / 0 0 / 0	0 / 214 (0.00%) 0 / 0 0 / 0	1 / 500 (0.20%) 0 / 1 0 / 0
VENTRICULAR DYSFUNCTION alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 358 (0.00%) 0 / 0 0 / 0	1 / 214 (0.47%) 0 / 1 0 / 0	0 / 500 (0.00%) 0 / 0 0 / 0
Nervous system disorders APHASIA alternative dictionary used: MedDRA 17			

subjects affected / exposed	0 / 358 (0.00%)	1 / 214 (0.47%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CENTRAL NERVOUS SYSTEM LESION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CEREBRAL HAEMORRHAGE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	2 / 214 (0.93%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	1 / 2	0 / 0
CEREBRAL INFARCTION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	1 / 214 (0.47%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CEREBRAL ISCHAEMIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	1 / 214 (0.47%)	3 / 500 (0.60%)
occurrences causally related to treatment / all	0 / 0	1 / 1	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CEREBROVASCULAR ACCIDENT			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	2 / 358 (0.56%)	1 / 214 (0.47%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 2	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CONVULSION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	1 / 214 (0.47%)	4 / 500 (0.80%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

DIZZINESS alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 0 / 358 (0.00%) 0 / 0 0 / 0	 1 / 214 (0.47%) 1 / 1 0 / 0	 0 / 500 (0.00%) 0 / 0 0 / 0
DYSARTHRIA alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 358 (0.28%) 1 / 1 0 / 0	 0 / 214 (0.00%) 0 / 0 0 / 0	 0 / 500 (0.00%) 0 / 0 0 / 0
ENCEPHALOPATHY alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 0 / 358 (0.00%) 0 / 0 0 / 0	 1 / 214 (0.47%) 1 / 1 0 / 0	 0 / 500 (0.00%) 0 / 0 0 / 0
GRAND MAL CONVULSION alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 0 / 358 (0.00%) 0 / 0 0 / 0	 1 / 214 (0.47%) 0 / 1 0 / 0	 0 / 500 (0.00%) 0 / 0 0 / 0
HEMIPARESIS alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 0 / 358 (0.00%) 0 / 0 0 / 0	 0 / 214 (0.00%) 0 / 0 0 / 0	 1 / 500 (0.20%) 0 / 1 0 / 0
ISCHAEMIC STROKE alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 358 (0.28%) 1 / 1 0 / 0	 1 / 214 (0.47%) 1 / 1 1 / 1	 0 / 500 (0.00%) 0 / 0 0 / 0
METABOLIC ENCEPHALOPATHY alternative dictionary used: MedDRA 17			

subjects affected / exposed	1 / 358 (0.28%)	0 / 214 (0.00%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MONOPARESIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NERVOUS SYSTEM DISORDER			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NEURALGIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NEUROLOGICAL SYMPTOM			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	1 / 214 (0.47%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NEUROPATHY PERIPHERAL			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	1 / 214 (0.47%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PARAESTHESIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 358 (0.28%)	0 / 214 (0.00%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

PERIPHERAL SENSORY NEUROPATHY			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
REVERSIBLE POSTERIOR LEUKOENCEPHALOPATHY SYNDROME			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SPINAL CORD COMPRESSION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 358 (0.28%)	0 / 214 (0.00%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUBARACHNOID HAEMORRHAGE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SYNCOPE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TRANSIENT ISCHAEMIC ATTACK			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 358 (0.28%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
ANAEMIA			
alternative dictionary used:			

MedDRA 17				
subjects affected / exposed	2 / 358 (0.56%)	0 / 214 (0.00%)	3 / 500 (0.60%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	3 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0	
COOMBS POSITIVE HAEMOLYTIC ANAEMIA				
alternative dictionary used: MedDRA 17				
subjects affected / exposed	1 / 358 (0.28%)	0 / 214 (0.00%)	0 / 500 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0	
DISSEMINATED INTRAVASCULAR COAGULATION				
alternative dictionary used: MedDRA 17				
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0	
FEBRILE NEUTROPENIA				
alternative dictionary used: MedDRA 17				
subjects affected / exposed	3 / 358 (0.84%)	4 / 214 (1.87%)	4 / 500 (0.80%)	
occurrences causally related to treatment / all	1 / 3	5 / 5	4 / 4	
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0	
GRANULOCYTOPENIA				
alternative dictionary used: MedDRA 17				
subjects affected / exposed	2 / 358 (0.56%)	1 / 214 (0.47%)	1 / 500 (0.20%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0	
LEUKOPENIA				
alternative dictionary used: MedDRA 17				
subjects affected / exposed	1 / 358 (0.28%)	0 / 214 (0.00%)	0 / 500 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0	
LYMPHOPENIA				
alternative dictionary used: MedDRA 17				

subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NEUTROPENIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	3 / 358 (0.84%)	0 / 214 (0.00%)	7 / 500 (1.40%)
occurrences causally related to treatment / all	1 / 3	0 / 0	4 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PANCYTOPENIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	1 / 214 (0.47%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
THROMBOCYTOPENIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	7 / 358 (1.96%)	0 / 214 (0.00%)	11 / 500 (2.20%)
occurrences causally related to treatment / all	6 / 7	0 / 0	10 / 11
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
RETINAL HAEMORRHAGE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	1 / 214 (0.47%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RETINAL VEIN OCCLUSION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
ABDOMINAL HERNIA			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ABDOMINAL PAIN			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	3 / 358 (0.84%)	3 / 214 (1.40%)	3 / 500 (0.60%)
occurrences causally related to treatment / all	1 / 4	0 / 4	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ABDOMINAL PAIN UPPER			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	1 / 214 (0.47%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ANAL HAEMORRHAGE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ASCITES			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 358 (0.28%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COLITIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	1 / 214 (0.47%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COLONIC OBSTRUCTION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

CONSTIPATION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 358 (0.28%)	0 / 214 (0.00%)	4 / 500 (0.80%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIARRHOEA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	11 / 358 (3.07%)	14 / 214 (6.54%)	34 / 500 (6.80%)
occurrences causally related to treatment / all	13 / 13	15 / 16	35 / 39
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DUODENAL ULCER PERFORATION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 358 (0.28%)	0 / 214 (0.00%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DYSPHAGIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 358 (0.28%)	0 / 214 (0.00%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTRITIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	2 / 500 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROINTESTINAL FISTULA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROINTESTINAL HAEMORRHAGE			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	2 / 358 (0.56%)	3 / 214 (1.40%)	4 / 500 (0.80%)
occurrences causally related to treatment / all	1 / 2	3 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROINTESTINAL NECROSIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 358 (0.28%)	0 / 214 (0.00%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROINTESTINAL OBSTRUCTION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 358 (0.28%)	1 / 214 (0.47%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROINTESTINAL PERFORATION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMATEMESIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 358 (0.28%)	0 / 214 (0.00%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMATOCHYZIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 358 (0.28%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMORRHOIDS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	1 / 214 (0.47%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

ILEITIS				
alternative dictionary used: MedDRA 17				
subjects affected / exposed	0 / 358 (0.00%)	1 / 214 (0.47%)	0 / 500 (0.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0	
ILEUS				
alternative dictionary used: MedDRA 17				
subjects affected / exposed	4 / 358 (1.12%)	1 / 214 (0.47%)	5 / 500 (1.00%)	
occurrences causally related to treatment / all	1 / 4	1 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0	
ILEUS PARALYTIC				
alternative dictionary used: MedDRA 17				
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0	
INGUINAL HERNIA				
alternative dictionary used: MedDRA 17				
subjects affected / exposed	1 / 358 (0.28%)	0 / 214 (0.00%)	0 / 500 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0	
INTESTINAL FISTULA				
alternative dictionary used: MedDRA 17				
subjects affected / exposed	1 / 358 (0.28%)	0 / 214 (0.00%)	0 / 500 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0	
INTESTINAL HAEMORRHAGE				
alternative dictionary used: MedDRA 17				
subjects affected / exposed	2 / 358 (0.56%)	1 / 214 (0.47%)	1 / 500 (0.20%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0	
INTESTINAL OBSTRUCTION				
alternative dictionary used: MedDRA 17				

subjects affected / exposed	4 / 358 (1.12%)	3 / 214 (1.40%)	8 / 500 (1.60%)
occurrences causally related to treatment / all	2 / 4	0 / 3	1 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INTESTINAL PERFORATION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	1 / 214 (0.47%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LARGE INTESTINE PERFORATION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LOWER GASTROINTESTINAL HAEMORRHAGE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	1 / 214 (0.47%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MECHANICAL ILEUS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 358 (0.28%)	1 / 214 (0.47%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
MELAENA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	1 / 214 (0.47%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MESENTERIC VEIN THROMBOSIS			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	0 / 358 (0.00%)	1 / 214 (0.47%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NAUSEA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	3 / 214 (1.40%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	4 / 4	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PANCREATITIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 358 (0.28%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PEPTIC ULCER			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	1 / 214 (0.47%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERITONITIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	1 / 214 (0.47%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PROCTALGIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PROCTOCOLITIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	1 / 214 (0.47%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

RECTAL HAEMORRHAGE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 358 (0.28%)	0 / 214 (0.00%)	2 / 500 (0.40%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RECTAL OBSTRUCTION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	1 / 214 (0.47%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SMALL INTESTINAL OBSTRUCTION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 358 (0.28%)	1 / 214 (0.47%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
STOMATITIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 358 (0.28%)	3 / 214 (1.40%)	2 / 500 (0.40%)
occurrences causally related to treatment / all	1 / 1	2 / 3	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUBILEUS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	2 / 358 (0.56%)	3 / 214 (1.40%)	2 / 500 (0.40%)
occurrences causally related to treatment / all	1 / 3	1 / 3	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VARICES OESOPHAGEAL			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VOMITING			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	8 / 358 (2.23%)	5 / 214 (2.34%)	7 / 500 (1.40%)
occurrences causally related to treatment / all	7 / 9	4 / 5	7 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
BILE DUCT OBSTRUCTION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	1 / 214 (0.47%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHOLANGITIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHOLECYSTITIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	2 / 500 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHOLECYSTITIS ACUTE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	2 / 500 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHOLESTASIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEPATIC FUNCTION ABNORMAL			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	1 / 358 (0.28%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEPATORENAL FAILURE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 358 (0.28%)	0 / 214 (0.00%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
HYPERBILIRUBINAEMIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	3 / 358 (0.84%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	2 / 3	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
JAUNDICE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 358 (0.28%)	0 / 214 (0.00%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
PETECHIAE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PURPURA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
AZOTAEMIA			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMATURIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NEPHROTIC SYNDROME			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 358 (0.28%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PROTEINURIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	3 / 500 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RENAL FAILURE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	5 / 214 (2.34%)	3 / 500 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 5	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 1
RENAL FAILURE ACUTE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 358 (0.28%)	2 / 214 (0.93%)	2 / 500 (0.40%)
occurrences causally related to treatment / all	0 / 1	1 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
RENAL FAILURE CHRONIC			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 358 (0.28%)	0 / 214 (0.00%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

RENAL IMPAIRMENT alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 358 (0.28%) 0 / 1 0 / 0	0 / 214 (0.00%) 0 / 0 0 / 0	3 / 500 (0.60%) 2 / 3 0 / 0
URETERIC OBSTRUCTION alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 358 (0.00%) 0 / 0 0 / 0	0 / 214 (0.00%) 0 / 0 0 / 0	1 / 500 (0.20%) 0 / 1 0 / 0
URETHRAL STENOSIS alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 358 (0.28%) 0 / 2 0 / 0	0 / 214 (0.00%) 0 / 0 0 / 0	0 / 500 (0.00%) 0 / 0 0 / 0
URINARY BLADDER HAEMORRHAGE alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 358 (0.00%) 0 / 0 0 / 0	0 / 214 (0.00%) 0 / 0 0 / 0	1 / 500 (0.20%) 0 / 2 0 / 0
URINARY RETENTION alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 358 (0.00%) 0 / 0 0 / 0	0 / 214 (0.00%) 0 / 0 0 / 0	1 / 500 (0.20%) 0 / 1 0 / 0
Endocrine disorders HYPOTHYROIDISM alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 358 (0.00%) 0 / 0 0 / 0	2 / 214 (0.93%) 2 / 2 0 / 0	0 / 500 (0.00%) 0 / 0 0 / 0
THYROIDITIS alternative dictionary used: MedDRA 17			

subjects affected / exposed	0 / 358 (0.00%)	1 / 214 (0.47%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 358 (0.28%)	1 / 214 (0.47%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BACK PAIN			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 358 (0.28%)	0 / 214 (0.00%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GROIN PAIN			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MUSCULAR WEAKNESS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 358 (0.28%)	1 / 214 (0.47%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OSTEOARTHRITIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PAIN IN EXTREMITY			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	2 / 500 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PATHOLOGICAL FRACTURE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	1 / 214 (0.47%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
ABDOMINAL WALL ABSCESS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	1 / 214 (0.47%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ACUTE SINUSITIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
AMOEBIASIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	1 / 214 (0.47%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
AMOEBIC DYSENTERY			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	1 / 214 (0.47%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
APPENDICITIS PERFORATED			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	0 / 358 (0.00%)	1 / 214 (0.47%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BLASTOCYSTIS INFECTION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BRONCHITIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	1 / 214 (0.47%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BRONCHOPNEUMONIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 358 (0.28%)	0 / 214 (0.00%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
CAMPYLOBACTER INTESTINAL INFECTION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CATHETER RELATED INFECTION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 358 (0.28%)	1 / 214 (0.47%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CATHETER SEPSIS			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CATHETER SITE INFECTION alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	1 / 214 (0.47%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CELLULITIS alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 358 (0.28%)	0 / 214 (0.00%)	2 / 500 (0.40%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CENTRAL LINE INFECTION alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 358 (0.28%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COLOSTOMY INFECTION alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DENGUE FEVER alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROENTERITIS alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	2 / 214 (0.93%)	3 / 500 (0.60%)
occurrences causally related to treatment / all	0 / 0	2 / 2	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

INFECTED EPIDERMAL CYST alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LOWER RESPIRATORY TRACT INFECTION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	1 / 214 (0.47%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LUNG ABSCESS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	1 / 214 (0.47%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MENINGITIS BACTERIAL			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ORAL CANDIDIASIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 358 (0.28%)	0 / 214 (0.00%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	8 / 358 (2.23%)	3 / 214 (1.40%)	7 / 500 (1.40%)
occurrences causally related to treatment / all	4 / 8	0 / 3	4 / 8
deaths causally related to treatment / all	1 / 2	0 / 0	0 / 3
PYELONEPHRITIS			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYOTHORAX			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SCROTAL ABSCESS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 358 (0.28%)	0 / 214 (0.00%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SEPSIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	3 / 358 (0.84%)	3 / 214 (1.40%)	4 / 500 (0.80%)
occurrences causally related to treatment / all	0 / 3	2 / 3	2 / 4
deaths causally related to treatment / all	0 / 1	2 / 3	1 / 1
SEPTIC SHOCK			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 358 (0.28%)	0 / 214 (0.00%)	3 / 500 (0.60%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	1 / 2
STAPHYLOCOCCAL SEPSIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
UPPER RESPIRATORY TRACT INFECTION			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	1 / 358 (0.28%)	0 / 214 (0.00%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY TRACT INFECTION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	2 / 358 (0.56%)	0 / 214 (0.00%)	6 / 500 (1.20%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VIRAL UPPER RESPIRATORY TRACT INFECTION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
WOUND INFECTION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 358 (0.28%)	0 / 214 (0.00%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
DECREASED APPETITE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 358 (0.28%)	0 / 214 (0.00%)	3 / 500 (0.60%)
occurrences causally related to treatment / all	0 / 1	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEHYDRATION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	7 / 358 (1.96%)	8 / 214 (3.74%)	14 / 500 (2.80%)
occurrences causally related to treatment / all	7 / 8	6 / 9	12 / 16
deaths causally related to treatment / all	0 / 0	1 / 2	1 / 1
DIABETES MELLITUS			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERAMMONAEMIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	1 / 214 (0.47%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERTRIGLYCERIDAEMIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOKALAEMIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	1 / 358 (0.28%)	1 / 214 (0.47%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPONATRAEMIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	2 / 358 (0.56%)	0 / 214 (0.00%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOPROTEINAEMIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	0 / 358 (0.00%)	0 / 214 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo	cediranib 30 mg	cediranib 20 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	341 / 358 (95.25%)	209 / 214 (97.66%)	485 / 500 (97.00%)
Vascular disorders			
HYPERTENSION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	41 / 358 (11.45%)	96 / 214 (44.86%)	226 / 500 (45.20%)
occurrences (all)	49	128	297
PHLEBITIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	18 / 358 (5.03%)	7 / 214 (3.27%)	19 / 500 (3.80%)
occurrences (all)	20	7	24
General disorders and administration site conditions			
ASTHENIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	45 / 358 (12.57%)	32 / 214 (14.95%)	74 / 500 (14.80%)
occurrences (all)	64	41	114
FATIGUE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	104 / 358 (29.05%)	80 / 214 (37.38%)	200 / 500 (40.00%)
occurrences (all)	169	133	322
OEDEMA PERIPHERAL			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	46 / 358 (12.85%)	22 / 214 (10.28%)	53 / 500 (10.60%)
occurrences (all)	58	34	57
PYREXIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	60 / 358 (16.76%)	31 / 214 (14.49%)	76 / 500 (15.20%)
occurrences (all)	104	54	110
Immune system disorders			
DRUG HYPERSENSITIVITY			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	19 / 358 (5.31%)	6 / 214 (2.80%)	24 / 500 (4.80%)
occurrences (all)	29	7	31
Respiratory, thoracic and mediastinal disorders			

COUGH alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences (all)	35 / 358 (9.78%) 39	24 / 214 (11.21%) 31	50 / 500 (10.00%) 57
DYSPHONIA alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences (all)	4 / 358 (1.12%) 9	39 / 214 (18.22%) 46	67 / 500 (13.40%) 80
DYSPNOEA alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences (all)	24 / 358 (6.70%) 26	14 / 214 (6.54%) 18	29 / 500 (5.80%) 31
EPISTAXIS alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences (all)	31 / 358 (8.66%) 42	37 / 214 (17.29%) 49	63 / 500 (12.60%) 86
HICCUPS alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences (all)	8 / 358 (2.23%) 10	11 / 214 (5.14%) 11	23 / 500 (4.60%) 37
OROPHARYNGEAL PAIN alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences (all)	6 / 358 (1.68%) 6	12 / 214 (5.61%) 12	28 / 500 (5.60%) 35
Psychiatric disorders INSOMNIA alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences (all)	27 / 358 (7.54%) 30	15 / 214 (7.01%) 19	50 / 500 (10.00%) 65
Investigations ALANINE AMINOTRANSFERASE INCREASED alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences (all) ASPARTATE AMINOTRANSFERASE	15 / 358 (4.19%) 22	11 / 214 (5.14%) 13	33 / 500 (6.60%) 56

INCREASED			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	18 / 358 (5.03%)	9 / 214 (4.21%)	33 / 500 (6.60%)
occurrences (all)	28	12	59
PLATELET COUNT DECREASED			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	17 / 358 (4.75%)	6 / 214 (2.80%)	33 / 500 (6.60%)
occurrences (all)	26	12	54
WEIGHT DECREASED			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	18 / 358 (5.03%)	28 / 214 (13.08%)	63 / 500 (12.60%)
occurrences (all)	19	30	78
Nervous system disorders			
DIZZINESS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	23 / 358 (6.42%)	19 / 214 (8.88%)	52 / 500 (10.40%)
occurrences (all)	29	28	63
DYSAESTHESIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	11 / 358 (3.07%)	13 / 214 (6.07%)	16 / 500 (3.20%)
occurrences (all)	18	32	19
DYSGEUSIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	25 / 358 (6.98%)	14 / 214 (6.54%)	26 / 500 (5.20%)
occurrences (all)	35	17	34
HEADACHE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	34 / 358 (9.50%)	35 / 214 (16.36%)	70 / 500 (14.00%)
occurrences (all)	60	54	111
HYPOAESTHESIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	17 / 358 (4.75%)	7 / 214 (3.27%)	38 / 500 (7.60%)
occurrences (all)	24	7	56
NEUROPATHY PERIPHERAL			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	64 / 358 (17.88%)	24 / 214 (11.21%)	77 / 500 (15.40%)
occurrences (all)	127	46	161
PARAESTHESIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	85 / 358 (23.74%)	49 / 214 (22.90%)	97 / 500 (19.40%)
occurrences (all)	174	100	180
PERIPHERAL SENSORY NEUROPATHY			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	89 / 358 (24.86%)	45 / 214 (21.03%)	141 / 500 (28.20%)
occurrences (all)	158	69	260
Blood and lymphatic system disorders			
ANAEMIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	43 / 358 (12.01%)	24 / 214 (11.21%)	40 / 500 (8.00%)
occurrences (all)	61	28	51
GRANULOCYTOPENIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	9 / 358 (2.51%)	3 / 214 (1.40%)	28 / 500 (5.60%)
occurrences (all)	24	14	61
LEUKOPENIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	39 / 358 (10.89%)	15 / 214 (7.01%)	84 / 500 (16.80%)
occurrences (all)	86	34	264
NEUTROPENIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	75 / 358 (20.95%)	49 / 214 (22.90%)	138 / 500 (27.60%)
occurrences (all)	182	73	421
THROMBOCYTOPENIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	84 / 358 (23.46%)	56 / 214 (26.17%)	139 / 500 (27.80%)
occurrences (all)	144	85	296
Gastrointestinal disorders			
ABDOMINAL DISTENSION			
alternative dictionary used: MedDRA 17			

subjects affected / exposed	19 / 358 (5.31%)	6 / 214 (2.80%)	27 / 500 (5.40%)
occurrences (all)	20	6	37
ABDOMINAL PAIN			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	78 / 358 (21.79%)	32 / 214 (14.95%)	134 / 500 (26.80%)
occurrences (all)	126	40	199
ABDOMINAL PAIN UPPER			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	28 / 358 (7.82%)	24 / 214 (11.21%)	58 / 500 (11.60%)
occurrences (all)	38	27	85
CONSTIPATION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	78 / 358 (21.79%)	34 / 214 (15.89%)	85 / 500 (17.00%)
occurrences (all)	124	58	117
DIARRHOEA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	165 / 358 (46.09%)	147 / 214 (68.69%)	346 / 500 (69.20%)
occurrences (all)	339	444	1044
DYSPEPSIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	20 / 358 (5.59%)	18 / 214 (8.41%)	35 / 500 (7.00%)
occurrences (all)	25	21	45
FLATULENCE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	12 / 358 (3.35%)	4 / 214 (1.87%)	27 / 500 (5.40%)
occurrences (all)	12	4	27
NAUSEA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	169 / 358 (47.21%)	92 / 214 (42.99%)	256 / 500 (51.20%)
occurrences (all)	429	217	675
STOMATITIS			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	48 / 358 (13.41%)	59 / 214 (27.57%)	118 / 500 (23.60%)
occurrences (all)	73	102	187

VOMITING alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences (all)	126 / 358 (35.20%) 287	83 / 214 (38.79%) 187	230 / 500 (46.00%) 544
Skin and subcutaneous tissue disorders ALOPECIA alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences (all) DRY SKIN alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences (all) PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences (all) RASH alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences (all) SKIN HYPERPIGMENTATION alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences (all)	22 / 358 (6.15%) 23 11 / 358 (3.07%) 11 57 / 358 (15.92%) 87 19 / 358 (5.31%) 21 25 / 358 (6.98%) 26	18 / 214 (8.41%) 20 14 / 214 (6.54%) 15 53 / 214 (24.77%) 75 9 / 214 (4.21%) 13 9 / 214 (4.21%) 10	38 / 500 (7.60%) 39 16 / 500 (3.20%) 18 123 / 500 (24.60%) 167 33 / 500 (6.60%) 41 34 / 500 (6.80%) 35
Renal and urinary disorders PROTEINURIA alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences (all)	12 / 358 (3.35%) 16	20 / 214 (9.35%) 40	60 / 500 (12.00%) 101
Endocrine disorders HYPOTHYROIDISM alternative dictionary used: MedDRA 17 subjects affected / exposed occurrences (all)	8 / 358 (2.23%) 8	28 / 214 (13.08%) 29	42 / 500 (8.40%) 43

Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	14 / 358 (3.91%)	15 / 214 (7.01%)	34 / 500 (6.80%)
occurrences (all)	14	19	46
BACK PAIN			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	19 / 358 (5.31%)	17 / 214 (7.94%)	41 / 500 (8.20%)
occurrences (all)	21	21	48
MUSCULOSKELETAL PAIN			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	12 / 358 (3.35%)	13 / 214 (6.07%)	22 / 500 (4.40%)
occurrences (all)	14	15	27
PAIN IN EXTREMITY			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	14 / 358 (3.91%)	14 / 214 (6.54%)	48 / 500 (9.60%)
occurrences (all)	14	15	61
Infections and infestations			
URINARY TRACT INFECTION			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	14 / 358 (3.91%)	15 / 214 (7.01%)	40 / 500 (8.00%)
occurrences (all)	15	23	62
Metabolism and nutrition disorders			
DECREASED APPETITE			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	125 / 358 (34.92%)	92 / 214 (42.99%)	229 / 500 (45.80%)
occurrences (all)	231	155	396
HYPOKALAEMIA			
alternative dictionary used: MedDRA 17			
subjects affected / exposed	22 / 358 (6.15%)	19 / 214 (8.88%)	58 / 500 (11.60%)
occurrences (all)	37	29	95

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