Clinical trial results:
A Randomized, Double-Blind, Phase 3 Study of Docetaxel and Ramucirumab versus Docetaxel and Placebo in the Treatment of Stage IV Non-Small Cell Lung Cancer Following Disease Progression after One Prior Platinum-Based Therapy

Summary

EudraCT number	2010-021297-11
Trial protocol	DE NL ES IT NO AT SE GR GB HU
Global end of trial date	10 August 2016

Results information

Result version number	v1 (current)
This version publication date	28 July 2017
First version publication date	28 July 2017

Trial information

Trial identification

Sponsor protocol code	13852

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01168973
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Number: 13852 , Trial Alias: I4T-MC-JVBA

Notes:

Sponsors

Sponsor organisation name	Eli Lilly and Company
Sponsor organisation address	Lilly Corporate Center, Indianapolis, United States, 46285
Public contact	Eli Lilly and Company, Available Mon - Fri 9 AM - 5 PM EST, 1 877-285-4559,
Scientific contact	Eli Lilly and Company, Available Mon - Fri 9 AM - 5 PM EST, 1 877-CTLilly,

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	10 August 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 August 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of the study is to compare the survival of participants who receive chemotherapy and ramucirumab versus chemotherapy alone as second line treatment for NSCLC after prior first line platinum-based chemotherapy.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 December 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 308
Country: Number of subjects enrolled	Taiwan: 27
Country: Number of subjects enrolled	Greece: 44
Country: Number of subjects enrolled	Spain: 50
Country: Number of subjects enrolled	Israel: 22
Country: Number of subjects enrolled	Russian Federation: 61
Country: Number of subjects enrolled	Italy: 54
Country: Number of subjects enrolled	Switzerland: 26
Country: Number of subjects enrolled	India: 55
Country: Number of subjects enrolled	France: 45
Country: Number of subjects enrolled	Puerto Rico: 3
Country: Number of subjects enrolled	Netherlands: 31
Country: Number of subjects enrolled	Korea, Republic of: 62
Country: Number of subjects enrolled	Turkey: 45
Country: Number of subjects enrolled	Austria: 20
Country: Number of subjects enrolled	United Kingdom: 38
Country: Number of subjects enrolled	Hungary: 13
Country: Number of subjects enrolled	Mexico: 31
Country: Number of subjects enrolled	Canada: 19

Country: Number of subjects enrolled	Argentina: 33
Country: Number of subjects enrolled	Brazil: 7
Country: Number of subjects enrolled	Poland: 63
Country: Number of subjects enrolled	Romania: 77
Country: Number of subjects enrolled	Norway: 13
Country: Number of subjects enrolled	Germany: 82
Country: Number of subjects enrolled	New Zealand: 7
Country: Number of subjects enrolled	Sweden: 17
Worldwide total number of subjects	1253
EEA total number of subjects	547

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)	798
From 65 to 84 years	453
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants who died, due to any cause, or were alive at the end of the study but off study drug were considered to have completed the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Ramucirumab and Docetaxel

Arm description:

On Day 1 of each 21-day cycle, participants received ramucirumab drug product (DP) followed by docetaxel. Treatment continued until disease progression, unacceptable toxicity, or other withdrawal criteria were met.

- Ramucirumab DP: 10 milligrams per kilogram (mg/kg) administered intravenously.
- Docetaxel: 75 milligrams per square meter (mg/m^2) (60 mg/m^2 for the countries of Korea and Taiwan only, with protocol amendment dated 22 May 2012) administered intravenously.

Arm type	Experimental
Investigational medicinal product name	Ramucirumab
Investigational medicinal product code	
Other name	IMC 1121B, LY3009806
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

10 milligrams per kilogram (mg/kg) administered intravenously (IV) on Day 1 of 21-day cycle until disease progression, unacceptable toxicity, or another withdrawal criterion is met.

Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

75 milligrams per square meter (mg/m^2) (60 mg/m^2 for the countries of Korea and Taiwan only with protocol amendment dated 22 May 2012) administered IV on Day 1 of 21-day cycle until disease progression, unacceptable toxicity, or another withdrawal criterion is met.

Arm title	Placebo and Docetaxel

Arm description:

On Day 1 of each 21-day cycle, participants received placebo followed by docetaxel. Treatment continued until disease progression, unacceptable toxicity, or other withdrawal criteria were met.

- Placebo (matching Ramucirumab DP): 10 mg/kg administered intravenously.
- Docetaxel: 75 mg/m^2 (60 mg/m^2 for the countries of Korea and Taiwan only, with protocol amendment dated 22 May 2012) administered intravenously.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered IV on Day 1 of 21-day cycle until disease progression, unacceptable toxicity, or another withdrawal criterion is met.

Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

75 milligrams per square meter (mg/m^2) (60 mg/m^2 for the countries of Korea and Taiwan only with protocol amendment dated 22 May 2012) administered IV on Day 1 of 21-day cycle until disease progression, unacceptable toxicity, or another withdrawal criterion is met.

Number of subjects in period 1	Ramucirumab and Docetaxel	Placebo and Docetaxel
Started	628	625
Received any quantity of any study drug	624	621
Completed	15	14
Not completed	613	611
Adverse event, serious fatal	42	45
Consent withdrawn by subject	90	53
Physician decision	37	19
Protocol Criterion Not Met and Deviation	7	9
Adverse event, non-fatal	94	55
Progressive Disease	341	429
Sponsor Decision	2	1

Baseline characteristics

Reporting groups

Reporting group title	Ramucirumab and Docetaxel

Reporting group description:

On Day 1 of each 21-day cycle, participants received ramucirumab drug product (DP) followed by docetaxel. Treatment continued until disease progression, unacceptable toxicity, or other withdrawal criteria were met.

- Ramucirumab DP: 10 milligrams per kilogram (mg/kg) administered intravenously.
- Docetaxel: 75 milligrams per square meter (mg/m^2) (60 mg/m^2 for the countries of Korea and Taiwan only, with protocol amendment dated 22 May 2012) administered intravenously.

Reporting group title	Placebo and Docetaxel

Reporting group description:

On Day 1 of each 21-day cycle, participants received placebo followed by docetaxel. Treatment continued until disease progression, unacceptable toxicity, or other withdrawal criteria were met.

- Placebo (matching Ramucirumab DP): 10 mg/kg administered intravenously.
- Docetaxel: 75 mg/m^2 (60 mg/m^2 for the countries of Korea and Taiwan only, with protocol amendment dated 22 May 2012) administered intravenously.

Reporting group values	Ramucirumab and Docetaxel	Placebo and Docetaxel	Total
Number of subjects	628	625	1253
Age Categorical Units:			
Between 18 and 65 years	391	407	798
>=65 years	237	218	455
Gender, Male/Female Units:			
Female	209	210	419
Male	419	415	834
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	43	53	96
Not Hispanic or Latino	387	380	767
Unknown or Not Reported	198	192	390
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	9	20	29
Asian	74	86	160
Native Hawaiian or Other Pacific Islander	1	0	1
Black or African American	17	16	33
White	526	503	1029
More than one race	0	0	0
Unknown or Not Reported	1	0	1

End points

End points reporting groups

Reporting group title	Ramucirumab and Docetaxel

Reporting group description:

On Day 1 of each 21-day cycle, participants received ramucirumab drug product (DP) followed by docetaxel. Treatment continued until disease progression, unacceptable toxicity, or other withdrawal criteria were met.

- Ramucirumab DP: 10 milligrams per kilogram (mg/kg) administered intravenously.
- Docetaxel: 75 milligrams per square meter (mg/m^2) (60 mg/m^2 for the countries of Korea and Taiwan only, with protocol amendment dated 22 May 2012) administered intravenously.

Reporting group title	Placebo and Docetaxel

Reporting group description:

On Day 1 of each 21-day cycle, participants received placebo followed by docetaxel. Treatment continued until disease progression, unacceptable toxicity, or other withdrawal criteria were met.

- Placebo (matching Ramucirumab DP): 10 mg/kg administered intravenously.
- Docetaxel: 75 mg/m^2 (60 mg/m^2 for the countries of Korea and Taiwan only, with protocol amendment dated 22 May 2012) administered intravenously.

Primary: Overall survival

End point title	Overall survival[1]

End point description:

Overall survival was the time from randomization until the date of death from any cause. Participants who were alive at the end of the follow-up period (or lost to followup) were censored on the last date the participant was known to be alive.

End point type	Primary

End point timeframe:

Randomization to date of death from any cause (up to 34 months)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Per the protocol, this study was considered complete when the final analysis of the primary endpoint was performed. After the primary analysis, only ramucirumab participants who were on study therapy and experiencing ongoing clinical benefit (that is, no disease progression) continued to receive their current study therapy in the extension period. Hence no additional analyses of OS will be conducted after the primary since only a small subset of participants were being followed.

End point values	Ramucirumab and Docetaxel	Placebo and Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	628	625		
Units: months				
median (confidence interval 95%)	10.5 (9.5 to 11.2)	9.1 (8.4 to 10)		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Participants achieved an objective response if they had a best overall response of partial response (PR) or complete response (CR). According to RECIST v1.1, PR was defined as at least a 30% decrease in the sum of the diameters of target lesions (including the short axes of any target lymph node), taking as reference the baseline sum diameter; CR was the disappearance of all non-nodal target lesions, with the short axes of any target lymph node reduced to <10 mm, the disappearance of all nontarget lesions, and the normalization of tumor marker levels [if tumor markers were initially above the upper limit of normal (ULN)]. The percentage of participants who achieved an objective response=(number of participants with CR or PR)/(number of participants assessed)*100.

End point type	Secondary

End point timeframe:

Baseline to measured PD (up to 29 months)

End point values	Ramucirumab and Docetaxel	Placebo and Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	628	625		
Units: percentage of participants				
number (confidence interval 95%)	22.9 (19.7 to 26.4)	13.6 (11 to 16.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) Time

End point title	Progression-Free Survival (PFS) Time

End point description:

PFS time was the time from randomization until the date of objectively determined progressive disease (PD) or death due to any cause, whichever occurred first. According to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1), PD was at least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study. In addition to the 20% relative increase, the sum must have also demonstrated an absolute increase of at least 5 millimeters (mm). The appearance of 1 or more new lesions and/or unequivocal progression of existing nontarget lesions was also considered progression. Participants without objectively determined PD who were alive at the end of the follow-up period (or lost to followup) were censored on the date of the participant's last complete radiographic tumor assessment; if no baseline or post-baseline radiologic assessment was available, the participant was censored at the date of randomization.

End point type	Secondary

End point timeframe:

Randomization to measured PD or date of death from any cause (up to 29 months)

End point values	Ramucirumab and Docetaxel	Placebo and Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	628	625		
Units: months				
median (confidence interval 95%)	4.5 (4.2 to 5.3)	3 (2.8 to 3.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants achieving disease control (Disease Control Rate)

End point title	Percentage of participants achieving disease control (Disease Control Rate)

End point description:

Participants achieved disease control if they had a best overall response of PR, CR or stable disease (SD). According to RECIST v1.1, PR was defined as at least a 30% decrease in the sum of the diameters of target lesions (including the short axes of any target lymph node), taking as reference the baseline sum diameter; CR was the disappearance of all non-nodal target lesions, with the short axes of any target lymph node reduced to <10 mm, the disappearance of all nontarget lesions, and the normalization of tumor marker levels (if tumor markers were initially above the ULN). SD was neither sufficient shrinkage to qualify as PR nor sufficient increase to qualify as PD, taking as reference the smallest sum diameter since treatment started. The percentage of participants who achieved disease control=(number of participants with CR, PR, or SD)/(number of participants assessed)*100.

End point type	Secondary

End point timeframe:

Baseline to measured PD (up to 29 months)

End point values	Ramucirumab and Docetaxel	Placebo and Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	628	625		
Units: percentage of participants				
number (confidence interval 95%)	64 (60.1 to 67.8)	52.6 (48.6 to 56.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Improvement on Lung Cancer Symptom Scale (LCSS)

End point title	Maximum Improvement on Lung Cancer Symptom Scale (LCSS)

End point description:

The LCSS consisted of 9 items: 6 items focused on lung cancer symptoms [loss of appetite, fatigue, cough, dyspnea (shortness of breath), hemoptysis (blood in sputum), and pain] and 3 items were global items (symptom distress, interference with activity level, and global quality of life). Participant responses to each item were measured using visual analogue scales (VAS) with 100-mm lines. A higher

score for any item represented a higher level of symptoms/problems. The Average Symptom Burden Index (ASBI) was the mean of the 6 symptom items of the LCSS, and the Total LCSS was the mean of all 9 LCSS items. ASBI and Total LCSS were not computed for a participant if he/she had 1 or more missing values for the 6 and 9 items, respectively. Maximum improvement in LCSS scores, ASBI, and Total LCSS score was the largest decrease from baseline for each variable, which was the smallest (most negative or smallest positive) non-missing value among all change from baseline values for each variable.

End point type	Secondary

End point timeframe:

Baseline, Day 21 of each cycle, and 30 days following the last infusion (up to Cycle 38, 21 days/cycle)
Population: Randomized participants grouped according to assigned treatment at randomization, with a baseline and at least 1 post-baseline LCSS Score.

End point values	Ramucirumab and Docetaxel	Placebo and Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	476	477		
Units: mm				
arithmetic mean (standard deviation)				
Loss of Appetite (n=473, 471)	-10.9 (± 26.11)	-11 (± 26.22)		
Fatigue (n=473, 472)	-12.1 (± 23.86)	-12 (± 27.29)		
Cough (n=476, 473)	-13.8 (± 24.28)	-14.3 (± 26.28)		
Dyspnea (n=472, 477)	-11 (± 23.01)	-10.5 (± 24.31)		
Hemoptysis (n=475, 475)	-1.4 (± 8.89)	-1.1 (± 8.79)		
Pain (n=476, 475)	-11.3 (± 23.62)	-11.5 (± 24.85)		
Symptom Distress (n=474, 472)	-10.7 (± 23.37)	-12.2 (± 26.25)		
Interference With Activity Level (n=474, 472)	-8.5 (± 24.13)	-7.9 (± 24.95)		
Global Quality of Life (n=467, 469)	-10.4 (± 22.68)	-8.9 (± 23.23)		
ASBI (n=455, 456)	-6.1 (± 13.75)	-6.9 (± 14.5)		
Total LCSS (n=446, 446)	-5.2 (± 13.75)	-6.4 (± 14.66)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to 30-Day follow-Up visit on European Quality of Life Questionnaire-5 Dimension (EQ-5D) Health State Scores

End point title	Change from baseline to 30-Day follow-Up visit on European Quality of Life Questionnaire-5 Dimension (EQ-5D) Health State Scores

End point description:

The EQ-5D is a quality-of-life instrument that consists of 2 parts. The first part (Health State Index score) allowed participants to rate their health state in 5 health domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression using a scale from 1 to 3 (no problem, some problems, and extreme problems, respectively). These combinations of attributes were converted into a

weighted Health State Index score according to a United Kingdom population-based algorithm; the possible values for the Health State Index score ranged from -0.59 (severe problems in all 5 dimensions) to 1.0 (no problem in any dimension). The second part of the EQ-5D was a VAS that allowed participants to rate their present health condition. Possible EQ-5D VAS scores ranged from 0 (worst imaginable health state) to 100 (best imaginable health state).

End point type	Secondary

End point timeframe:

Baseline, 30 days following last infusion (up to Cycle 38, 21 days/cycle)

Population: Randomized participants grouped according to their assigned treatment at randomization, who had an EQ-5D assessment at a baseline and 30 days post treatment.

End point values	Ramucirumab and Docetaxel	Placebo and Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	272[2]	272[3]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Health State Index Score (n=266, 272)	-0.14 (± 0.308)	-0.126 (± 0.294)		
Health State VAS Score (n=272, 254)	-5.9 (± 21.02)	-6.1 (± 20.31)		

Notes:

[2] - Participants who had an EQ-5D assessment at a baseline and 30 days post treatment.

[3] - Participants who had an EQ-5D assessment at a baseline and 30 days post treatment.

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum and Minimum Serum Concentrations (Cmax and Cmin) of Ramucirumab

End point title	Maximum and Minimum Serum Concentrations (Cmax and Cmin) of Ramucirumab[4]

End point description:

Participants assigned to the ramucirumab and docetaxel arm at randomization, who had evaluable ramucirumab pharmacokinetic (PK) data to calculate Cmax and Cmin.

End point type	Secondary

End point timeframe:

Prior to infusion and 1 hour following infusion for Cycles 3 and 5 (21 days/cycle)

Notes:

[4] - 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 is analyzing the ramucirumab PK data; not applicable for placebo arm.

End point values	Ramucirumab and Docetaxel			
Subject group type	Reporting group			
Number of subjects analysed	594[5]			
Units: micrograms per milliliter (mcg/mL)				
geometric mean (geometric coefficient of variation)				

Cmax at Cycle 3	262 (± 30)			
Cmin at Cycle 3	28.3 (± 65)			
Cmax at Cycle 5	237 (± 38)			
Cmin at Cycle 5	38.4 (± 63)			

Notes:

[5] - Participants who had evaluable ramucirumab PK data calculate Cmax and Cmin.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with anti-Ramucirumab antibodies

End point title	Number of Participants with anti-Ramucirumab antibodies

End point description:

The number of participants who had treatment-emergent or follow-up emergent anti-drug antibodies (ADA) is reported. Participants with treatment-emergent ADA were defined as participants who had any sample from baseline through Cycle 5 pre-infusion that was a 4-fold increase (2 dilution increase) in immunogenicity titer over the baseline titer, or participants who tested negative at baseline and positive post-baseline (at titer of ≥1:20). Participants with follow-up emergent ADA were defined as participants who had any sample during 30 days post last infusion that was a 4-fold increase (2 dilution increase) in immunogenicity titer over the baseline titer.

Population: Randomized participants who received any quantity of study treatment, grouped by the treatment they actually received, who had a baseline and at least 1 post-baseline ADA assessment.

End point type	Secondary

End point timeframe:

Baseline, prior to infusion for Cycles 3 and 5, and 30 days following last infusion (up to Cycle 38, 21 days/cycle)

End point values	Ramucirumab and Docetaxel	Placebo and Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	599[6]	598[7]		
Units: participants				
number (not applicable)				
Treatment-Emergent ADA (n=599, 598)	9	16		
Follow-Up Emergent ADA (n=506, 481)	9	16		

Notes:

[6] - Participants who had a baseline and at least 1 post-baseline ADA assessment.

[7] - Participants who had a baseline and at least 1 post-baseline ADA assessment.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Participants Who Had Treatment-Emergent Adverse Events (TEAEs) or Died

End point title	Number of Participants Who Had Treatment-Emergent Adverse Events (TEAEs) or Died

End point description:

Data presented are the number of participants who experienced at least 1 TEAE, Grade 3, 4, or 5 TEAE, treatment-emergent serious adverse event (SAE), TEAE leading to discontinuation of study treatment (ramucirumab/placebo or docetaxel), and TEAE leading to death. Clinically significant events were

defined as treatment-emergent SAEs and other non-serious adverse events (AEs) regardless of causality. A summary of SAEs and other non-serious AEs, regardless of causality, is located in the Reported Adverse Events module.

Safety population: Randomized participants who received any quantity of study drug, grouped by the treatment they actually received.

End point type	Other pre-specified

End point timeframe:

First infusion up to 30 days following last infusion (up to Cycle 38, 21 days/cycle)

End point values	Ramucirumab and Docetaxel	Placebo and Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	627[8]	618[9]		
Units: participants				
number (not applicable)				
At least 1 TEAE	613	594		
At least 1 Grade 3, 4, or 5 TEAE	495	444		
At least 1 treatment-emergent SAE	269	262		
TEAE leading to study drug discontinuation	58	32		
TEAE leading to death	34	35		
Deaths While On Treatment	428	451		
Deaths During 30 Days Post Last Dose	53	58		

Notes:

[8] - Participants who received any quantity of study drug, grouped by treatment they actually received.

[9] - Participants who received any quantity of study drug, grouped by treatment they actually received.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Randomization through 30 days following last infusion (up to Cycle 38, 21 days/cycle)

Adverse event reporting additional description:

Safety Population: All randomized participants who received any quantity of study treatment, grouped by the treatment they actually received.

Three participants randomized to placebo and docetaxel received 1 dose of ramucirumab in error.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Ramucirumab and Docetaxel

Reporting group description:

On Day 1 of each 21-day cycle, participants received ramucirumab DP followed by docetaxel. Treatment continued until disease progression, unacceptable toxicity, or other withdrawal criteria were met.

- Ramucirumab DP: 10 mg/kg administered intravenously.
- Docetaxel: 75 mg/m^2 (60 mg/m^2 for the countries of Korea and Taiwan only, with protocol amendment dated 22 May 2012) administered intravenously.

Reporting group title	Placebo and Docetaxel

Reporting group description:

On Day 1 of each 21-day cycle, participants received placebo followed by docetaxel. Treatment continued until disease progression, unacceptable toxicity, or other withdrawal criteria were met.

- Placebo (matching Ramucirumab DP): 10 mg/kg administered intravenously.
- Docetaxel: 75 mg/m^2 (60 mg/m^2 for the countries of Korea and Taiwan only, with protocol amendment dated 22 May 2012) administered intravenously.

Serious adverse events	Ramucirumab and Docetaxel	Placebo and Docetaxel	
Total subjects affected by serious adverse events			
subjects affected / exposed	284 / 627 (45.30%)	281 / 618 (45.47%)	
number of deaths (all causes)	34	41	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Intracranial tumour haemorrhage			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 627 (0.32%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphangiosis carcinomatosa			

alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant ascites			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant pleural effusion			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	5 / 618 (0.81%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bone			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 627 (0.32%)	3 / 618 (0.49%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to liver			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	2 / 618 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to meninges			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	2 / 627 (0.32%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to spine			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 627 (0.32%)	3 / 618 (0.49%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastatic neoplasm			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastatic pain			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	5 / 627 (0.80%)	7 / 618 (1.13%)	
occurrences causally related to treatment / all	0 / 6	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion malignant			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestine carcinoma			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour associated fever			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Tumour compression			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour necrosis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm rupture			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Deep vein thrombosis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 627 (0.32%)	2 / 618 (0.32%)	
occurrences causally related to treatment / all	1 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	3 / 627 (0.48%)	4 / 618 (0.65%)	
occurrences causally related to treatment / all	2 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iliac artery occlusion			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jugular vein thrombosis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery aneurysm			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior vena cava syndrome			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Venous thrombosis limb			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Hospitalisation			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung lobectomy			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Adverse drug reaction			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	3 / 627 (0.48%)	4 / 618 (0.65%)	
occurrences causally related to treatment / all	11 / 11	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	2 / 618 (0.32%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			

alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	5 / 627 (0.80%)	3 / 618 (0.49%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 5	0 / 3	
Disease progression			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	2 / 618 (0.32%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	12 / 627 (1.91%)	6 / 618 (0.97%)	
occurrences causally related to treatment / all	14 / 18	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	5 / 627 (0.80%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	4 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 627 (0.32%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	1 / 627 (0.16%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 627 (0.32%)	3 / 618 (0.49%)	
occurrences causally related to treatment / all	1 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 627 (0.32%)	2 / 618 (0.32%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral swelling			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	10 / 627 (1.59%)	10 / 618 (1.62%)	
occurrences causally related to treatment / all	3 / 10	1 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Immune system disorders			
Anaphylactic shock			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug hypersensitivity			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	2 / 618 (0.32%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 627 (0.32%)	2 / 618 (0.32%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	1 / 2	0 / 2	
Acute respiratory failure			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	6 / 618 (0.97%)	
occurrences causally related to treatment / all	0 / 1	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Aspiration			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 627 (0.32%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atelectasis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			

alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catarrh			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	5 / 627 (0.80%)	4 / 618 (0.65%)	
occurrences causally related to treatment / all	2 / 7	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	11 / 627 (1.75%)	26 / 618 (4.21%)	
occurrences causally related to treatment / all	2 / 12	3 / 32	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	7 / 627 (1.12%)	6 / 618 (0.97%)	
occurrences causally related to treatment / all	7 / 9	3 / 7	
deaths causally related to treatment / all	1 / 2	0 / 2	
Haemothorax			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiccups			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrothorax			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	3 / 618 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infiltration			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Oropharyngeal pain			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	9 / 627 (1.44%)	21 / 618 (3.40%)	
occurrences causally related to treatment / all	0 / 10	4 / 23	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumomediastinum			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pneumothorax			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	5 / 627 (0.80%)	3 / 618 (0.49%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 627 (0.32%)	3 / 618 (0.49%)	
occurrences causally related to treatment / all	1 / 2	2 / 3	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pneumothorax spontaneous			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	2 / 627 (0.32%)	2 / 618 (0.32%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary bulla			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary congestion			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	8 / 627 (1.28%)	12 / 618 (1.94%)	
occurrences causally related to treatment / all	4 / 8	8 / 13	
deaths causally related to treatment / all	1 / 2	0 / 0	
Pulmonary haemorrhage			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	4 / 627 (0.64%)	4 / 618 (0.65%)	
occurrences causally related to treatment / all	2 / 4	1 / 5	
deaths causally related to treatment / all	2 / 4	1 / 3	
Pulmonary oedema			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory acidosis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Respiratory arrest			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory disorder			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	2 / 618 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Respiratory failure			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	3 / 627 (0.48%)	9 / 618 (1.46%)	
occurrences causally related to treatment / all	0 / 3	1 / 10	
deaths causally related to treatment / all	0 / 2	1 / 5	
Respiratory tract haemorrhage			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Tachypnoea			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	7 / 627 (1.12%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	3 / 7	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Conversion disorder			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Echolalia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mania			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Mental status changes			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood alkaline phosphatase increased			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diagnostic aspiration			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
International normalised ratio increased			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
alternative dictionary used:			

MedDRA 16.1			
subjects affected / exposed	9 / 627 (1.44%)	3 / 618 (0.49%)	
occurrences causally related to treatment / all	10 / 10	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 627 (0.32%)	2 / 618 (0.32%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	3 / 627 (0.48%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax traumatic			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	3 / 627 (0.48%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pubis fracture			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suture related complication			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Traumatic arthropathy			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Tracheo-oesophageal fistula			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Arrhythmia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	6 / 627 (0.96%)	2 / 618 (0.32%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial tachycardia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 627 (0.32%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			

alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 627 (0.32%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	2 / 2	0 / 1	
Cardiac failure			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac tamponade			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 627 (0.32%)	2 / 618 (0.32%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 2	1 / 2	
Coronary artery occlusion			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pericardial effusion			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	6 / 618 (0.97%)	
occurrences causally related to treatment / all	0 / 2	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 627 (0.32%)	3 / 618 (0.49%)	
occurrences causally related to treatment / all	0 / 2	1 / 4	
deaths causally related to treatment / all	0 / 0	1 / 1	
Tachycardia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular arrhythmia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Aphasia			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain oedema			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cognitive disorder			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Convulsion			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	3 / 627 (0.48%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	2 / 618 (0.32%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiplegia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Ivth nerve paralysis			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine with aura			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraparesis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peroneal nerve palsy			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Radicular syndrome			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Senile dementia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stupor			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	4 / 627 (0.64%)	4 / 618 (0.65%)	
occurrences causally related to treatment / all	3 / 4	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic encephalopathy			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tremor			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal cord paresis			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	10 / 627 (1.59%)	14 / 618 (2.27%)	
occurrences causally related to treatment / all	15 / 16	11 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	86 / 627 (13.72%)	51 / 618 (8.25%)	
occurrences causally related to treatment / all	104 / 104	55 / 56	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	5 / 627 (0.80%)	10 / 618 (1.62%)	
occurrences causally related to treatment / all	6 / 6	14 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	30 / 627 (4.78%)	27 / 618 (4.37%)	
occurrences causally related to treatment / all	37 / 38	33 / 33	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	3 / 627 (0.48%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	3 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Diplopia			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal vein thrombosis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	3 / 627 (0.48%)	7 / 618 (1.13%)	
occurrences causally related to treatment / all	0 / 3	2 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal inflammation			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 627 (0.32%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	2 / 618 (0.32%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Diarrhoea			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	13 / 627 (2.07%)	9 / 618 (1.46%)	
occurrences causally related to treatment / all	12 / 13	5 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticular perforation			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 627 (0.32%)	2 / 618 (0.32%)	
occurrences causally related to treatment / all	1 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 627 (0.32%)	3 / 618 (0.49%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Enteritis alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	2 / 618 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Gastrointestinal inflammation alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gingival bleeding alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileal fistula			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 627 (0.32%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Large intestinal obstruction alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 627 (0.32%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	7 / 627 (1.12%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	5 / 8	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic colitis alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal fistula alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal haemorrhage alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Oesophageal pain			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal perforation			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peptic ulcer haemorrhage			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Rectal haemorrhage			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	2 / 618 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal perforation			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	14 / 627 (2.23%)	2 / 618 (0.32%)	
occurrences causally related to treatment / all	16 / 16	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Vomiting			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	6 / 627 (0.96%)	8 / 618 (1.29%)	
occurrences causally related to treatment / all	5 / 6	4 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatitis acute			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pruritus			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psoriasis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous emphysema			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute prerenal failure			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	4 / 627 (0.64%)	2 / 618 (0.32%)	
occurrences causally related to treatment / all	5 / 8	1 / 2	
deaths causally related to treatment / all	1 / 1	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 627 (0.32%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pathological fracture			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	2 / 618 (0.32%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal disorder			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Anal abscess			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 627 (0.32%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	3 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary tract infection			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	2 / 627 (0.32%)	6 / 618 (0.97%)	
occurrences causally related to treatment / all	0 / 2	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis moraxella			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Candida infection			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	3 / 627 (0.48%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis staphylococcal			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Clostridium difficile colitis alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 627 (0.32%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	2 / 618 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	3 / 627 (0.48%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	2 / 627 (0.32%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	7 / 627 (1.12%)	8 / 618 (1.29%)	
occurrences causally related to treatment / all	4 / 7	3 / 8	
deaths causally related to treatment / all	0 / 0	0 / 1	
Localised infection			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 627 (0.32%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	3 / 627 (0.48%)	5 / 618 (0.81%)	
occurrences causally related to treatment / all	1 / 6	4 / 5	
deaths causally related to treatment / all	0 / 2	0 / 0	
Neutropenic infection			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 627 (0.32%)	2 / 618 (0.32%)	
occurrences causally related to treatment / all	1 / 2	2 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	

Oral candidiasis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 627 (0.32%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral herpes			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paronychia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic abscess			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 627 (0.32%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	3 / 627 (0.48%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	3 / 618 (0.49%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	37 / 627 (5.90%)	41 / 618 (6.63%)	
occurrences causally related to treatment / all	18 / 43	7 / 48	
deaths causally related to treatment / all	2 / 3	1 / 6	
Pneumonia bacterial			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 627 (0.32%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia escherichia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pneumococcal			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	2 / 618 (0.32%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia staphylococcal			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonia streptococcal alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Postoperative wound infection alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	3 / 627 (0.48%)	3 / 618 (0.49%)	
occurrences causally related to treatment / all	2 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	3 / 627 (0.48%)	2 / 618 (0.32%)	
occurrences causally related to treatment / all	3 / 3	2 / 2	
deaths causally related to treatment / all	1 / 1	1 / 1	
Septic shock alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 627 (0.32%)	3 / 618 (0.49%)	
occurrences causally related to treatment / all	2 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Staphylococcal sepsis alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stenotrophomonas sepsis alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Upper respiratory tract infection			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	2 / 627 (0.32%)	4 / 618 (0.65%)	
occurrences causally related to treatment / all	1 / 2	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Decreased appetite			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	15 / 627 (2.39%)	15 / 618 (2.43%)	
occurrences causally related to treatment / all	14 / 17	11 / 18	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	2 / 627 (0.32%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	2 / 618 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	2 / 618 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 627 (0.00%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 627 (0.16%)	1 / 618 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	4 / 627 (0.64%)	3 / 618 (0.49%)	
occurrences causally related to treatment / all	3 / 4	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	3 / 627 (0.48%)	0 / 618 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Ramucirumab and Docetaxel	Placebo and Docetaxel	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	601 / 627 (95.85%)	583 / 618 (94.34%)	
Investigations			
Neutrophil count decreased			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	112 / 627 (17.86%)	89 / 618 (14.40%)	
occurrences (all)	281	193	
Platelet count decreased			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	36 / 627 (5.74%)	9 / 618 (1.46%)	
occurrences (all)	104	20	
Weight decreased			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	67 / 627 (10.69%)	49 / 618 (7.93%)	
occurrences (all)	84	56	
White blood cell count decreased			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	58 / 627 (9.25%)	50 / 618 (8.09%)	
occurrences (all)	148	219	
Vascular disorders			
Hypertension			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	67 / 627 (10.69%)	29 / 618 (4.69%)	
occurrences (all)	129	107	
Nervous system disorders			
Dizziness			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	43 / 627 (6.86%)	46 / 618 (7.44%)	
occurrences (all)	54	52	

Dysgeusia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	69 / 627 (11.00%)	46 / 618 (7.44%)	
occurrences (all)	83	55	
Headache			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	66 / 627 (10.53%)	65 / 618 (10.52%)	
occurrences (all)	88	78	
Paraesthesia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	38 / 627 (6.06%)	36 / 618 (5.83%)	
occurrences (all)	49	46	
Peripheral sensory neuropathy			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	74 / 627 (11.80%)	60 / 618 (9.71%)	
occurrences (all)	121	102	
Blood and lymphatic system disorders			
Anaemia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	135 / 627 (21.53%)	174 / 618 (28.16%)	
occurrences (all)	306	399	
Leukopenia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	79 / 627 (12.60%)	68 / 618 (11.00%)	
occurrences (all)	259	151	
Neutropenia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	228 / 627 (36.36%)	188 / 618 (30.42%)	
occurrences (all)	547	415	
Thrombocytopenia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	51 / 627 (8.13%)	27 / 618 (4.37%)	
occurrences (all)	114	48	
General disorders and administration site conditions			

Asthenia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	72 / 627 (11.48%)	65 / 618 (10.52%)	
occurrences (all)	178	127	
Fatigue			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	287 / 627 (45.77%)	260 / 618 (42.07%)	
occurrences (all)	623	524	
Mucosal inflammation			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	103 / 627 (16.43%)	43 / 618 (6.96%)	
occurrences (all)	167	53	
Oedema peripheral			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	107 / 627 (17.07%)	55 / 618 (8.90%)	
occurrences (all)	149	86	
Pain			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	35 / 627 (5.58%)	33 / 618 (5.34%)	
occurrences (all)	40	37	
Pyrexia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	100 / 627 (15.95%)	79 / 618 (12.78%)	
occurrences (all)	148	114	
Eye disorders			
Lacrimation increased			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	85 / 627 (13.56%)	29 / 618 (4.69%)	
occurrences (all)	100	31	
Gastrointestinal disorders			
Abdominal pain			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	56 / 627 (8.93%)	35 / 618 (5.66%)	
occurrences (all)	69	41	
Constipation			

alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	107 / 627 (17.07%)	110 / 618 (17.80%)	
occurrences (all)	135	132	
Diarrhoea			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	200 / 627 (31.90%)	175 / 618 (28.32%)	
occurrences (all)	338	226	
Dyspepsia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	37 / 627 (5.90%)	18 / 618 (2.91%)	
occurrences (all)	47	25	
Nausea			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	170 / 627 (27.11%)	173 / 618 (27.99%)	
occurrences (all)	236	256	
Stomatitis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	143 / 627 (22.81%)	81 / 618 (13.11%)	
occurrences (all)	245	104	
Vomiting			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	88 / 627 (14.04%)	86 / 618 (13.92%)	
occurrences (all)	117	119	
Respiratory, thoracic and mediastinal disorders			
Cough			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	137 / 627 (21.85%)	131 / 618 (21.20%)	
occurrences (all)	194	169	
Dysphonia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	38 / 627 (6.06%)	23 / 618 (3.72%)	
occurrences (all)	49	23	
Dyspnoea			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	150 / 627 (23.92%)	148 / 618 (23.95%)	
occurrences (all)	220	207	
Epistaxis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	116 / 627 (18.50%)	41 / 618 (6.63%)	
occurrences (all)	149	45	
Haemoptysis			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	36 / 627 (5.74%)	31 / 618 (5.02%)	
occurrences (all)	38	37	
Oropharyngeal pain			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	49 / 627 (7.81%)	30 / 618 (4.85%)	
occurrences (all)	65	39	
Productive cough			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	40 / 627 (6.38%)	34 / 618 (5.50%)	
occurrences (all)	61	41	
Skin and subcutaneous tissue disorders			
Alopecia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	163 / 627 (26.00%)	156 / 618 (25.24%)	
occurrences (all)	192	176	
Nail discolouration			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	41 / 627 (6.54%)	27 / 618 (4.37%)	
occurrences (all)	45	27	
Rash			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	44 / 627 (7.02%)	36 / 618 (5.83%)	
occurrences (all)	56	51	
Psychiatric disorders			
Insomnia			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed	69 / 627 (11.00%)	54 / 618 (8.74%)	
occurrences (all)	78	55	
Musculoskeletal and connective tissue disorders			
Arthralgia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	71 / 627 (11.32%)	51 / 618 (8.25%)	
occurrences (all)	110	86	
Back pain			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	73 / 627 (11.64%)	56 / 618 (9.06%)	
occurrences (all)	113	83	
Bone pain			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	31 / 627 (4.94%)	36 / 618 (5.83%)	
occurrences (all)	40	57	
Myalgia			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	79 / 627 (12.60%)	65 / 618 (10.52%)	
occurrences (all)	123	110	
Pain in extremity			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	50 / 627 (7.97%)	26 / 618 (4.21%)	
occurrences (all)	60	31	
Metabolism and nutrition disorders			
Decreased appetite			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	189 / 627 (30.14%)	163 / 618 (26.38%)	
occurrences (all)	290	221	
Dehydration			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	39 / 627 (6.22%)	24 / 618 (3.88%)	
occurrences (all)	47	31	
Hyperglycaemia			
alternative dictionary used: MedDRA 16.1			

subjects affected / exposed occurrences (all)	39 / 627 (6.22%) 83	25 / 618 (4.05%) 49	

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

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Three participants randomized to placebo and docetaxel received 1 dose of ramucirumab in error. They are included in the placebo and docetaxel arm in the ITT population and are included in the ramucirumab and docetaxel arm in the Safety population.

Notes: