Clinical trial results:
A Randomized, Multicenter, Double-Blind, Placebo-Controlled Phase 3 Study of Weekly Paclitaxel With or Without Ramucirumab (IMC-1121B) Drug Product in Patients With Metastatic Gastric Adenocarcinoma, Refractory to or Progressive After First-Line Therapy With Platinum and Fluoropyrimidine

Summary

EudraCT number	2010-020426-18
Trial protocol	DE ES HU RO FR GB AT LT PT EE IT BE BG
Global end of trial date	20 February 2017

Results information

Result version number	v1 (current)
This version publication date	05 March 2018
First version publication date	05 March 2018

Trial information

Trial identification

Sponsor protocol code	I4T-IE-JVBE

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01170663
WHO universal trial number (UTN)	-
Other trial identifiers	Trial ID: 13894

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 February 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 February 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is a Phase III randomized multicenter double-blind, placebo controlled trial evaluating the safety and efficacy of paclitaxel plus ramucirumab (IMC-1211B) drug product (DP) compared to paclitaxel plus placebo.

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	06 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	Portugal: 2
Country: Number of subjects enrolled	United States: 24
Country: Number of subjects enrolled	Estonia: 10
Country: Number of subjects enrolled	Taiwan: 30
Country: Number of subjects enrolled	Spain: 21
Country: Number of subjects enrolled	Russian Federation: 21
Country: Number of subjects enrolled	Chile: 4
Country: Number of subjects enrolled	Italy: 28
Country: Number of subjects enrolled	France: 34
Country: Number of subjects enrolled	Australia: 41
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 45
Country: Number of subjects enrolled	Lithuania: 12
Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	United Kingdom: 15
Country: Number of subjects enrolled	Hungary: 29
Country: Number of subjects enrolled	Mexico: 4
Country: Number of subjects enrolled	Argentina: 1
Country: Number of subjects enrolled	Poland: 33
Country: Number of subjects enrolled	Brazil: 35

Country: Number of subjects enrolled	Belgium: 26
Country: Number of subjects enrolled	Singapore: 5
Country: Number of subjects enrolled	Romania: 14
Country: Number of subjects enrolled	Bulgaria: 12
Country: Number of subjects enrolled	Germany: 40
Country: Number of subjects enrolled	Japan: 140
Country: Number of subjects enrolled	Hong Kong: 3
Country: Number of subjects enrolled	Israel: 30
Worldwide total number of subjects	665
EEA total number of subjects	282

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)	418
From 65 to 84 years	247
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

No Text Entered

Pre-assignment

Screening details:

One (1) participant was randomized to the placebo/paclitaxel group but had ramucirumab (IMC-1121B) in error. For the Intent-to-Treat (ITT) population this participant was included in the placebo/paclitaxel treatment group and for the Safety population (Pop) this participant was included in ramucirumab (IMC-1121B)/paclitaxel treatment group.

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	Investigator, Subject

Blinding implementation details:

Completers include participants that discontinued study drugs either due to progressive disease (PD), due to an adverse event or died due to any cause, but not necessarily had any survival-FU assessment done.

Arms

Are arms mutually exclusive?	Yes
Arm title	Ramucirumab (IMC-1211B) plus Paclitaxel

Arm description:

8 milligrams/kilogram (mg/kg) of ramucirumab (IMC-1121B) was administered by intravenous (IV) infusion on Days 1 and 15 in combination with 80 milligrams/square meter (mg/m²) paclitaxel administered by IV infusion on Days 1, 8, and 15 of a 28-day cycle.

Arm type	Experimental
Investigational medicinal product name	Ramucirumab
Investigational medicinal product code	
Other name	IMC-1211B
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

8 milligrams/kilogram (mg/kg) of ramucirumab (IMC-1121B) was administered by intravenous (IV) infusion on Days 1 and 15 in combination with 80 milligrams/square meter (mg/m²) paclitaxel administered by IV infusion on Days 1, 8, and 15 of a 28-day cycle.

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

Dosage and administration details:

8 milligrams/kilogram (mg/kg) of ramucirumab (IMC-1121B) was administered by intravenous (IV) infusion on Days 1 and 15 in combination with 80 milligrams/square meter (mg/m²) paclitaxel administered by IV infusion on Days 1, 8, and 15 of a 28-day cycle.

Arm title	Placebo plus Paclitaxel

Arm description:

Placebo was administered by IV infusion on Days 1 and 15, in combination with 80 mg/m² paclitaxel administered on Days 1, 8, and 15 of a 28-day cycle.

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:

Placebo was administered by IV infusion on Days 1 and 15, in combination with 80 mg/m² paclitaxel administered on Days 1, 8, and 15 of a 28-day cycle.

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

Dosage and administration details:

Placebo was administered by IV infusion on Days 1 and 15 in combination with 80 mg/m² paclitaxel administered by IV infusion on Days 1, 8, and 15 of a 28-day cycle.

Number of subjects in period 1	Ramucirumab (IMC-1211B) plus Paclitaxel	Placebo plus Paclitaxel
Started	330	335
Received any treatment (Safety Pop)	327	329
Completed	316	315
Not completed	14	20
Withdrawal of consent without follow-up	11	11
Lost to follow-up	3	9

Baseline characteristics

Reporting groups	
Reporting group title	Ramucirumab (IMC-1211B) plus Paclitaxel
Reporting group description:	
8 milligrams/kilogram (mg/kg) of ramucirumab (IMC-1121B) was administered by intravenous (IV) infusion on Days 1 and 15 in combination with 80 milligrams/square meter (mg/m²) paclitaxel administered by IV infusion on Days 1, 8, and 15 of a 28-day cycle.	
Reporting group title	Placebo plus Paclitaxel
Reporting group description:	
Placebo was administered by IV infusion on Days 1 and 15, in combination with 80 mg/m² paclitaxel administered on Days 1, 8, and 15 of a 28-day cycle.	

Reporting group values	Ramucirumab (IMC-1211B) plus Paclitaxel	Placebo plus Paclitaxel	Total
Number of subjects	330	335	665
Age Categorical Units: Participants			
<=18 years	0	0	0
Between 18 and 65 years	205	213	418
>=65 years	125	122	247
Age Continuous Units: years			
median	61	61	
full range (min-max)	25 to 83	24 to 84	-
Gender, Male/Female Units: Participants			
Female	101	92	193
Male	229	243	472
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	31	26	57
Not Hispanic or Latino	299	309	608
Unknown or Not Reported	0	0	0
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	0	1	1
Asian	110	121	231
Black or African American	6	6	12
White	208	199	407
More than one race	0	1	1
Other	6	7	13
Region of Enrollment Units: Subjects			
Portugal	2	0	2
United States	12	12	24
Estonia	5	5	10
Taiwan	14	16	30
Spain	8	13	21
Russian Federation	8	13	21

Chile	1	3	4
Italy	13	15	28
France	20	14	34
Australia	18	23	41
Korea, Republic of	23	22	45
Lithuania	6	6	12
Austria	4	2	6
United Kingdom	6	9	15
Hungary	20	9	29
Mexico	2	2	4
Argentina	1	0	1
Poland	15	18	33
Brazil	19	16	35
Belgium	12	14	26
Singapore	2	3	5
Romania	7	7	14
Bulgaria	7	5	12
Germany	20	20	40
Japan	68	72	140
Hong Kong	2	1	3
Israel	15	15	30

End points

End points reporting groups

Reporting group title	Ramucirumab (IMC-1211B) plus Paclitaxel
Reporting group description:	
8 milligrams/kilogram (mg/kg) of ramucirumab (IMC-1121B) was administered by intravenous (IV) infusion on Days 1 and 15 in combination with 80 milligrams/square meter (mg/m²) paclitaxel administered by IV infusion on Days 1, 8, and 15 of a 28-day cycle.	
Reporting group title	Placebo plus Paclitaxel
Reporting group description:	
Placebo was administered by IV infusion on Days 1 and 15, in combination with 80 mg/m² paclitaxel administered on Days 1, 8, and 15 of a 28-day cycle.	

Primary: Overall Survival Time (OS)

End point title	Overall Survival Time (OS)
End point description:	
OS time was measured from date of randomization to date of death from any cause. Participants who were not known to have died on or before the date of data cut-off, OS data was censored on the last date (on or before the cut-off date) the participant was known to be alive.	
End point type	Primary
End point timeframe:	
Randomization up to 27.5 months	

End point values	Ramucirumab (IMC-1211B) plus Paclitaxel	Placebo plus Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	330[1]	335[2]		
Units: months				
median (confidence interval 95%)	9.6 (8.5 to 10.8)	7.4 (6.3 to 8.4)		

Notes:

[1] - Participants censored: Ramucirumab (IMC-1211B) plus Paclitaxel =74, Placebo plus Paclitaxel =75.

[2] - Participants censored: Ramucirumab (IMC-1211B) plus Paclitaxel =74, Placebo plus Paclitaxel =75.

Statistical analyses

Statistical analysis title	Overall Survival Statistical Analysis
Comparison groups	Ramucirumab (IMC-1211B) plus Paclitaxel v Placebo plus Paclitaxel
Number of subjects included in analysis	665
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0169 [3]
Method	Stratified Log Rank Test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.807

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.678
upper limit	0.962

Notes:

[3] - Adjusted for stratification factors: geographic region, time-to-progression from start of first-line therapy and disease measurability.

Secondary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)

End point description:

PFS was measured from date of randomization to first radiographically documented progressive disease (PD) or death due to any cause. PD defined using Response Evaluation Criteria in Solid Tumors v1.1 (RECIST v1.1) as ≥20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this included the baseline sum if that is the smallest on study). The sum must also demonstrate an absolute increase of at least 5 mm. Participants who had no baseline or post baseline radiological tumor assessment were censored at date of randomization. Participants who had no tumor progression or death within 2 scan intervals following the last assessment were censored at the date of last radiographic tumor assessment. Participants who began new anticancer treatment and had no tumor progression were censored at date of assessment prior to initiation of new therapy. Participants lost to follow-up or withdrew consent were censored at the date of their last assessment.

End point type	Secondary

End point timeframe:

Randomization up to 22.2 months

End point values	Ramucirumab (IMC-1211B) plus Paclitaxel	Placebo plus Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	330[4]	335[5]		
Units: months				
median (confidence interval 95%)	4.4 (4.2 to 5.3)	2.9 (2.8 to 3.0)		

Notes:

[4] - Participants censored: Ramucirumab (IMC-1211B) plus Paclitaxel =51, Placebo plus Paclitaxel =39.

[5] - Participants censored: Ramucirumab (IMC-1211B) plus Paclitaxel =51, Placebo plus Paclitaxel =39.

Statistical analyses

Statistical analysis title	Progression-Free Survival Statistical Analysis
Comparison groups	Ramucirumab (IMC-1211B) plus Paclitaxel v Placebo plus Paclitaxel
Number of subjects included in analysis	665
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
Method	Stratified Log Rank Test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.635

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.536
upper limit	0.752

Notes:

[6] - Adjusted for stratification factors: geographic region, time-to-progression from start of first-line therapy and disease measurability.

Secondary: Time to Progressive Disease (TTP)

End point title	Time to Progressive Disease (TTP)

End point description:

TTP was defined as the time from randomization until date of radiographic progression using RECIST v1.1 criteria. PD was defined as having a ≥20% increase in sum of longest diameter (LD) of target lesions and at minimum 5 millimeters (mm) increase above nadir. Participants who did not progress or were lost to follow-up were censored at the date of last tumor assessment. Participants who had no baseline tumor assessment or no post baseline assessment and no death reported with 2 scan intervals post randomization were censored at date of randomization. Participants with no progression and not died within 2 scan intervals after last assessment were censored at date of last tumor assessment. Participants with no post baseline assessment or tumor progression but death reported within 2 scan intervals after randomization were censored at date of death.

End point type	Secondary

End point timeframe:

Baseline up to 22.2 months

End point values	Ramucirumab (IMC-1211B) plus Paclitaxel	Placebo plus Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	330[7]	335[8]		
Units: months				
median (confidence interval 95%)	5.52 (4.50 to 5.68)	3.02 (2.86 to 4.14)		

Notes:

[7] - Participants censored: Ramucirumab (IMC-1211B) plus Paclitaxel =107, Placebo plus Paclitaxel =94.

[8] - Participants censored: Ramucirumab (IMC-1211B) plus Paclitaxel =107, Placebo plus Paclitaxel =94.

Statistical analyses

Statistical analysis title	Time to Progression Statistical Analysis
Comparison groups	Ramucirumab (IMC-1211B) plus Paclitaxel v Placebo plus Paclitaxel
Number of subjects included in analysis	665
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [9]
Method	Stratified Log Rank Test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.596

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.494
upper limit	0.72

Notes:

[9] - Adjusted for stratification factors: geographic region, time-to-progression from start of first-line therapy and disease measurability.

Secondary: Best Overall Response (BOR) of Complete Response (CR), Partial Response (PR), Stable Disease (SD) or PD

End point title	Best Overall Response (BOR) of Complete Response (CR), Partial Response (PR), Stable Disease (SD) or PD

End point description:

BOR was defined as the best response across all time points from randomization until radiologically confirmed PD using RECIST, v1.1 criteria. CR was defined as the disappearance of all target and non-target lesions and any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm and normalization of tumor marker level of non-target lesions. PR was defined as having a ≥30% decrease in sum of LD of target lesions. PD was defined as having a ≥20% increase in sum of LD of target lesions and ≥5 mm increase above nadir. SD was defined as small changes that did not meet above criteria.

End point type	Secondary

End point timeframe:

Randomization up to 22.2 months

End point values	Ramucirumab (IMC-1211B) plus Paclitaxel	Placebo plus Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	330[10]	335[11]		
Units: percentage of participants				
number (not applicable)				
CR	0.6	0.3		
PR	27.3	15.8		
SD	52.1	47.5		
PD	13.0	24.8		
Not Evaluable	0.3	0.9		
No Tumor Response Evaluation	6.7	10.7		

Notes:

[10] - All randomized participants.

[11] - All randomized participants.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with CR or PR [Objective Response Rate (ORR)]

End point title	Percentage of Participants with CR or PR [Objective Response Rate (ORR)]

End point description:

ORR was the percentage of participants who had CR or PR defined using RECIST v1.1 criteria. CR was defined as the disappearance of all target and non-target lesions and any pathological lymph nodes

(whether target or non-target) must have reduction in short axis to <10 mm and normalization of tumor marker level of non-target lesions. PR was defined as having a ≥30% decrease in sum of LD of target lesions. Percentage of participants calculated as: (number of participants with CR + PR)/(total number of participants)*100.

End point type	Secondary

End point timeframe:

Randomization up to 22.2 months

End point values	Ramucirumab (IMC-1211B) plus Paclitaxel	Placebo plus Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	330[12]	335[13]		
Units: percentage of participants				
number (confidence interval 95%)	27.9 (23.3 to 33.0)	16.1 (12.6 to 20.4)		

Notes:

[12] - All randomized participants.

[13] - All randomized participants.

Statistical analyses

Statistical analysis title	Objective Response Rate Statistical Analysis
Comparison groups	Ramucirumab (IMC-1211B) plus Paclitaxel v Placebo plus Paclitaxel
Number of subjects included in analysis	665
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001 [14]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	2.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.45
upper limit	3.16

Notes:

[14] - Adjusted for stratification factors: geographic region, time-to-progression from the start of first-line therapy and disease measurability.

Secondary: Percentage of Participants with Anti-Ramucirumab Antibodies (Serum Anti-Ramucirumab Antibody Assessment) (Immunogenicity)

End point title	Percentage of Participants with Anti-Ramucirumab Antibodies (Serum Anti-Ramucirumab Antibody Assessment) (Immunogenicity)

End point description:

Participants who developed treatment-emergent antibody responses to Ramucirumab (IMC-1121B) after baseline.

End point type	Secondary

End point timeframe:

Prior to and after ramucirumab (IMC-1121B) infusion: Day 1 Cycles 1, 2 and 3 (28-day cycles) Doses 1, 4, 7 and 30-37 days after last dose of study therapy up to 103 weeks

End point values	Ramucirumab (IMC-1211B) plus Paclitaxel	Placebo plus Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	320[15]	323[16]		
Units: percentage of participants				
number (not applicable)	1.6	0.3		

Notes:

[15] - All randomized participants who received at least one dose of study drug and developed antibodies.
[16] - All randomized participants who received at least one dose of study drug and developed antibodies.

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Concentration (Cmax) after First Ramucirumab (IMC-1211B) Infusion

End point title	Maximum Concentration (Cmax) after First Ramucirumab (IMC-1211B) Infusion[17]

End point description:

The inter-patient variability is reported as the geometric coefficient of variation (%). Geometric mean and coefficient of variation (CV) is reported as a number and not a decimal or percentage.

End point type	Secondary

End point timeframe:

Cycle 1, Day 1, 1 hour post end of infusion (28-day cycles)

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: pharmacokinetics was not assessed for the placebo/paclitaxel arm.

End point values	Ramucirumab (IMC-1211B) plus Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	259[18]			
Units: micrograms/milliliter (µg/mL)				
geometric mean (geometric coefficient of variation)	146 (± 28)			

Notes:

[18] - All participants who received Ramucirumab (IMC-1121B) plus Paclitaxel and had Cmax observed.

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax after 4th Ramucirumab (IMC-1211B) Infusion

End point title	Cmax after 4th Ramucirumab (IMC-1211B) Infusion[19]

End point description:

The inter-patient variability is reported as the geometric coefficient of variation (%). Geometric mean and coefficient of variation (CV) is reported as a number and not a decimal or percentage.

End point type	Secondary

End point timeframe:

Cycle 2, Day 15 1 hour post end of infusion (28-day cycles)

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: pharmacokinetics was not assessed for the placebo/paclitaxel arm.

End point values	Ramucirumab (IMC-1211B) plus Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	200			
Units: µg/mL				
geometric mean (geometric coefficient of variation)	193 (± 34)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax after 7th Ramucirumab (IMC-1211B) Infusion

End point title	Cmax after 7th Ramucirumab (IMC-1211B) Infusion[20]

End point description:

The inter-patient variability is reported as the geometric coefficient of variation (%). Geometric mean and coefficient of variation (CV) is reported as a number and not a decimal or percentage.

End point type	Secondary

End point timeframe:

Cycle 4, Day 1, 1 hour post end of infusion (28-day cycles)

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: pharmacokinetics was not assessed for the placebo/paclitaxel arm.

End point values	Ramucirumab (IMC-1211B) plus Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	127[21]			
Units: µg/mL				
geometric mean (geometric coefficient of variation)	216 (± 30)			

Notes:

[21] - All participants who received Ramucirumab (IMC-1121B) plus Paclitaxel and had Cmax observations.

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum Concentration (Cmin) Prior to First Ramucirumab (IMC-1211B) Infusion

End point title	Minimum Concentration (Cmin) Prior to First Ramucirumab (IMC-1211B) Infusion[22]

End point description:

This outcome measure was included in error as the time point was before ramucirumab (IMC-1211B) was administered. Cmin was not analyzed.

End point type	Secondary

End point timeframe:

Cycle 1, Day 1 predose (28-day cycles)

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: pharmacokinetics was not assessed for the placebo/paclitaxel arm.

End point values	Ramucirumab (IMC-1211B) plus Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	0[23]			
Units: µg/mL				
geometric mean (geometric coefficient of variation)	()			

Notes:

[23] - Zero participants were analyzed and no data is available.

Statistical analyses

No statistical analyses for this end point

Secondary: Cmin Prior to 4th Ramucirumab (IMC-1211B) Infusion

End point title	Cmin Prior to 4th Ramucirumab (IMC-1211B) Infusion[24]

End point description:

The inter-patient variability is reported as the geometric coefficient of variation (%). Geometric mean and coefficient of variation (CV) is reported as a number and not a decimal or percentage.

End point type	Secondary

End point timeframe:

Cycle 2, Day 15 (28-day cycle)

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: pharmacokinetics was not assessed for the placebo/paclitaxel arm.

End point values	Ramucirumab (IMC-1211B) plus Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	203[25]			
Units: µg/mL				
geometric mean (geometric coefficient of variation)	45.0 (± 50)			

Notes:

[25] - All participants who received Ramucirumab (IMC-1121B) plus Paclitaxel and had Cmin observations.

Statistical analyses

No statistical analyses for this end point

Secondary: Cmin Prior to 7th Ramucirumab (IMC-1211B) Infusion

End point title	Cmin Prior to 7th Ramucirumab (IMC-1211B) Infusion[26]

End point description:

The inter-patient variability is reported as the geometric coefficient of variation (%). Geometric mean and coefficient of variation (CV) is reported as a number and not a decimal or percentage.

End point type	Secondary

End point timeframe:

Cycle 4, Day 1 (28-day cycles)

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: pharmacokinetics was not assessed for the placebo/paclitaxel arm.

End point values	Ramucirumab (IMC-1211B) plus Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	142[27]			
Units: µg/mL				
geometric mean (geometric coefficient of variation)	62.8 (± 47)			

Notes:

[27] - All participants who received Ramucirumab (IMC-1121B) plus Paclitaxel and had Cmin observations.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to End of Therapy in European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life: Questionnaire (QLQ-C30) in Global Health Status

End point title	Change from Baseline to End of Therapy in European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life: Questionnaire (QLQ-C30) in Global Health Status

End point description:

EORTC QLQ-C30 v3.0 is a 30-item, self-administered questionnaire with multidimensional scales assessing 15 domains (5 functional domains [physical, role, cognitive, emotional, and social], 9

symptom scales [fatigue, pain, nausea and vomiting, dyspnea, loss of appetite, insomnia, constipation and diarrhea, and financial difficulties] and global health status scale). 28 questions assessed on a 1 (not at all) to 4 (very much) scale and the remaining 2 questions used a 1 (poor) to 7 (excellent) scale. A linear transformation was applied to standardize the raw scores to range between 0 and 100 per developer guidelines. For the functional domains and global health status scale, higher scores represent a better level of functioning. For symptoms scales, higher scores represented a greater degree of symptoms.

End point type	Secondary

End point timeframe:

Baseline, end of therapy (up to 103 weeks)

End point values	Ramucirumab (IMC-1211B) plus Paclitaxel	Placebo plus Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	209[28]	202[29]		
Units: units on a scale				
arithmetic mean (standard deviation)	-13.5 (± 23.24)	-12.1 (± 24.81)		

Notes:

[28] - All randomized participants with global health status observations.

[29] - All randomized participants with global health status observations.

Statistical analyses

Statistical analysis title	Questionnaire Statistical Analysis
Comparison groups	Ramucirumab (IMC-1211B) plus Paclitaxel v Placebo plus Paclitaxel
Number of subjects included in analysis	411
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3973 [30]
Method	ANCOVA

Notes:

[30] - Analysis of covariance (ANCOVA) included treatment group, randomization stratification factors and baseline value of Global Health Status scale.

Secondary: Change from Baseline to End of Therapy in European Quality of Life Questionnaire-5 Dimension (EuroQol EQ-5D) Index Score

End point title	Change from Baseline to End of Therapy in European Quality of Life Questionnaire-5 Dimension (EuroQol EQ-5D) Index Score

End point description:

The EQ-5D is a generic, multidimensional, health status instrument. The profile allowed participants to rate their health state in 5 health domains: mobility, self-care, usual activities, pain/discomfort, and mood using a 3-level scale [1 (no problem), 2 (some problems), and 3 (major problems)]. These combinations of responses were converted into a weighted health-state Index Score according to the United Kingdom (UK) population-based algorithm. The possible values for the Index Score ranged from -0.59 (severe problems in all 5 dimensions) to 1.0 (no problem in any dimension). A negative change indicated a worsening of the participant's health status.

End point type	Secondary

End point timeframe:

Baseline, end of therapy (up to 103 weeks)

End point values	Ramucirumab (IMC-1211B) plus Paclitaxel	Placebo plus Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	205[31]	201[32]		
Units: units on a scale				
arithmetic mean (standard deviation)	-0.16 (± 0.279)	-0.19 (± 0.337)		

Notes:

[31] - All randomized participants with EQ-5D observations.

[32] - All randomized participants with EQ-5D observations.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Participants with Serious and Other Non-Serious Adverse Events (AE) and Who Died

End point title	Number of Participants with Serious and Other Non-Serious Adverse Events (AE) and Who Died

End point description:

Participants who died or who had clinically significant events defined as serious AEs (SAEs) and other non-serious AEs (regardless of causality). A summary of SAEs and other non-serious AEs, regardless of causality, is located in the Reported Adverse Events module.

End point type	Other pre-specified

End point timeframe:

Baseline up to 103 weeks and within 30 days of last dose of study drug

End point values	Ramucirumab (IMC-1211B) plus Paclitaxel	Placebo plus Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	327[33]	329[34]		
Units: participants				
number (not applicable)				
SAEs	161	146		
Other Non-serious AEs	324	321		
Died	37	52		

Notes:

[33] - All randomized participants who received at least one dose of study drug.

[34] - All randomized participants who received at least one dose of study drug.

Statistical analyses

No statistical analyses for this end point

Adverse events

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

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups	
Reporting group title	Paclitaxel plus Ramucirumab
Reporting group description: -	
Reporting group title	Paclitaxel plus Placebo
Reporting group description: -	

Serious adverse events	Paclitaxel plus Ramucirumab	Paclitaxel plus Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	161 / 327 (49.24%)	146 / 329 (44.38%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
brain cancer metastatic			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
cancer pain			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
malignant ascites			
alternative dictionary used: MedDRA 17.1			

subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
malignant neoplasm progression			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	48 / 327 (14.68%)	49 / 329 (14.89%)	
occurrences causally related to treatment / all	0 / 65	0 / 66	
deaths causally related to treatment / all	0 / 37	0 / 39	
malignant pleural effusion			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
metastases to central nervous system			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
metastases to liver			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
metastases to meninges			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
metastases to spine			
alternative dictionary used: MedDRA 17.1			

subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
rectal cancer			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
tumour pain			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
arteriosclerosis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
deep vein thrombosis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	2 / 327 (0.61%)	2 / 329 (0.61%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypotension			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	2 / 327 (0.61%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypovolaemic shock			
alternative dictionary used: MedDRA 17.1			

subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
vein disorder			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
vena cava thrombosis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
venous thrombosis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 327 (0.00%)	2 / 329 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
asthenia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	5 / 327 (1.53%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
chest pain			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
death			
alternative dictionary used: MedDRA 17.1			

subjects affected / exposed	1 / 327 (0.31%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
device dislocation			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
disease progression			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 327 (0.00%)	2 / 329 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
drowning			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
fatigue			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	5 / 327 (1.53%)	7 / 329 (2.13%)	
occurrences causally related to treatment / all	0 / 5	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
feeling abnormal			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
general physical health deterioration			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	8 / 327 (2.45%)	9 / 329 (2.74%)	
occurrences causally related to treatment / all	0 / 10	0 / 12	
deaths causally related to treatment / all	0 / 1	0 / 2	

injection site injury			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
multi-organ failure			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
oedema peripheral			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	3 / 327 (0.92%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pain			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	2 / 327 (0.61%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pyrexia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	8 / 327 (2.45%)	7 / 329 (2.13%)	
occurrences causally related to treatment / all	0 / 9	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
acute respiratory distress syndrome			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
aspiration			
alternative dictionary used: MedDRA 17.1			

subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
dyspnoea			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	3 / 327 (0.92%)	4 / 329 (1.22%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
gynaecomastia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed[1]	1 / 226 (0.44%)	0 / 237 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
haemoptysis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	2 / 327 (0.61%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypoxia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
interstitial lung disease			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 327 (0.00%)	3 / 329 (0.91%)	
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 17.1			
subjects affected / exposed	1 / 327 (0.31%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

pleural effusion			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	5 / 327 (1.53%)	4 / 329 (1.22%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
pneumonitis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pneumothorax			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pulmonary embolism			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	2 / 327 (0.61%)	6 / 329 (1.82%)	
occurrences causally related to treatment / all	0 / 3	0 / 8	
deaths causally related to treatment / all	0 / 1	0 / 2	
respiratory failure			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Investigations			
alanine aminotransferase increased			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
anticoagulation drug level above therapeutic			
alternative dictionary used: MedDRA 17.1			

subjects affected / exposed	1 / 327 (0.31%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
aspartate aminotransferase increased			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
blood creatinine increased			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
blood urea increased			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
gamma-glutamyltransferase increased			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
clavicle fracture			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
gastroenteritis radiation			
alternative dictionary used: MedDRA 17.1			

subjects affected / exposed	1 / 327 (0.31%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
incisional hernia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
spinal compression fracture			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
splenic rupture			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
pyloric stenosis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
acute coronary syndrome			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
angina pectoris			
alternative dictionary used: MedDRA 17.1			

subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
atrial fibrillation			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	3 / 327 (0.92%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
atrial flutter			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
atrial thrombosis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
cardiac failure			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
extrasystoles			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)	
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 17.1			
subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Nervous system disorders			
akathisia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)	
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 17.1			
subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
cerebral infarction			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
cerebrovascular accident			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
coma			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hydrocephalus			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
intracranial pressure increased			
alternative dictionary used: MedDRA 17.1			

subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
ischaemic stroke			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
spinal cord compression			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)	
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 17.1			
subjects affected / exposed	8 / 327 (2.45%)	7 / 329 (2.13%)	
occurrences causally related to treatment / all	0 / 8	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
disseminated intravascular coagulation			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
febrile neutropenia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	8 / 327 (2.45%)	5 / 329 (1.52%)	
occurrences causally related to treatment / all	0 / 8	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
leukopenia			
alternative dictionary used: MedDRA 17.1			

subjects affected / exposed	1 / 327 (0.31%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
neutropenia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	12 / 327 (3.67%)	4 / 329 (1.22%)	
occurrences causally related to treatment / all	0 / 17	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
hearing impaired			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
vertigo			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
cataract			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
lacrimation increased			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
abdominal pain			
alternative dictionary used: MedDRA 17.1			

subjects affected / exposed	10 / 327 (3.06%)	11 / 329 (3.34%)	
occurrences causally related to treatment / all	0 / 12	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
abdominal pain upper			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
anal haemorrhage			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
aphagia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ascites			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	5 / 327 (1.53%)	3 / 329 (0.91%)	
occurrences causally related to treatment / all	0 / 8	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
constipation			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 327 (0.00%)	2 / 329 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
diarrhoea			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	5 / 327 (1.53%)	2 / 329 (0.61%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

diverticular perforation				
alternative dictionary used: MedDRA 17.1				
subjects affected / exposed	1 / 327 (0.31%)	0 / 329 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
dysphagia				
alternative dictionary used: MedDRA 17.1				
subjects affected / exposed	4 / 327 (1.22%)	3 / 329 (0.91%)		
occurrences causally related to treatment / all	0 / 4	0 / 3		
deaths causally related to treatment / all	0 / 0	0 / 0		
gastric haemorrhage				
alternative dictionary used: MedDRA 17.1				
subjects affected / exposed	3 / 327 (0.92%)	2 / 329 (0.61%)		
occurrences causally related to treatment / all	0 / 3	0 / 2		
deaths causally related to treatment / all	0 / 0	0 / 0		
gastrointestinal haemorrhage				
alternative dictionary used: MedDRA 17.1				
subjects affected / exposed	4 / 327 (1.22%)	2 / 329 (0.61%)		
occurrences causally related to treatment / all	0 / 4	0 / 2		
deaths causally related to treatment / all	0 / 1	0 / 1		
gastrointestinal obstruction				
alternative dictionary used: MedDRA 17.1				
subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
gastrointestinal perforation				
alternative dictionary used: MedDRA 17.1				
subjects affected / exposed	2 / 327 (0.61%)	0 / 329 (0.00%)		
occurrences causally related to treatment / all	0 / 3	0 / 0		
deaths causally related to treatment / all	0 / 1	0 / 0		
haematemesis				
alternative dictionary used: MedDRA 17.1				

subjects affected / exposed	3 / 327 (0.92%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ileus			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	2 / 327 (0.61%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
ileus paralytic			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
intestinal ischaemia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
intestinal obstruction			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	6 / 327 (1.83%)	3 / 329 (0.91%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
intestinal perforation			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
malabsorption			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

melaena				
alternative dictionary used: MedDRA 17.1				
subjects affected / exposed	2 / 327 (0.61%)	0 / 329 (0.00%)		
occurrences causally related to treatment / all	0 / 2	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
mouth ulceration				
alternative dictionary used: MedDRA 17.1				
subjects affected / exposed	1 / 327 (0.31%)	0 / 329 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
nausea				
alternative dictionary used: MedDRA 17.1				
subjects affected / exposed	2 / 327 (0.61%)	5 / 329 (1.52%)		
occurrences causally related to treatment / all	0 / 3	0 / 6		
deaths causally related to treatment / all	0 / 0	0 / 0		
obstruction gastric				
alternative dictionary used: MedDRA 17.1				
subjects affected / exposed	1 / 327 (0.31%)	1 / 329 (0.30%)		
occurrences causally related to treatment / all	0 / 1	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
odynophagia				
alternative dictionary used: MedDRA 17.1				
subjects affected / exposed	1 / 327 (0.31%)	0 / 329 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
oesophageal food impaction				
alternative dictionary used: MedDRA 17.1				
subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
oesophageal haemorrhage				
alternative dictionary used: MedDRA 17.1				

subjects affected / exposed	1 / 327 (0.31%)	0 / 329 (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 17.1			
subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
oesophageal spasm			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
oesophageal stenosis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 327 (0.00%)	2 / 329 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
oesophageal ulcer			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)	
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 17.1			
subjects affected / exposed	2 / 327 (0.61%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pancreatitis acute			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

peritonitis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	5 / 327 (1.53%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pneumatosis intestinalis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
small intestinal obstruction			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	3 / 327 (0.92%)	4 / 329 (1.22%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
small intestinal stenosis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
subileus			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
upper gastrointestinal haemorrhage			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
vomiting			
alternative dictionary used: MedDRA 17.1			

subjects affected / exposed	7 / 327 (2.14%)	10 / 329 (3.04%)	
occurrences causally related to treatment / all	0 / 9	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
bile duct obstruction			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
cholangitis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
cholecystitis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	3 / 327 (0.92%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
cholecystitis acute			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	2 / 327 (0.61%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
jaundice			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
jaundice cholestatic			
alternative dictionary used: MedDRA 17.1			

subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
azotaemia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
dysuria			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hydronephrosis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	2 / 327 (0.61%)	2 / 329 (0.61%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
obstructive uropathy			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	0 / 329 (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 17.1			
subjects affected / exposed	2 / 327 (0.61%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
renal failure acute			
alternative dictionary used: MedDRA 17.1			

subjects affected / exposed	1 / 327 (0.31%)	2 / 329 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
urinary retention			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	2 / 327 (0.61%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
inappropriate antidiuretic hormone secretion			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
arthralgia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
back pain			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	2 / 329 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
flank pain			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
myalgia			
alternative dictionary used: MedDRA 17.1			

subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pain in extremity			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)	
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 17.1			
subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
anal abscess			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
appendicitis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
bacteraemia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
biliary sepsis			
alternative dictionary used: MedDRA 17.1			

subjects affected / exposed	1 / 327 (0.31%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
biliary tract infection			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
bronchopneumonia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	2 / 327 (0.61%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
cellulitis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 327 (0.00%)	2 / 329 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
device related infection			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	2 / 327 (0.61%)	3 / 329 (0.91%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
device related sepsis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
diarrhoea infectious			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

endocarditis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
herpes zoster			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
infection			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
influenza			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
lobar pneumonia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
localised infection			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
lower respiratory tract infection			
alternative dictionary used: MedDRA 17.1			

subjects affected / exposed	0 / 327 (0.00%)	2 / 329 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
lung infection			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	3 / 327 (0.92%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
neutropenic sepsis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
perirectal abscess			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
peritonitis bacterial			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	3 / 327 (0.92%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pneumonia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	3 / 327 (0.92%)	3 / 329 (0.91%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
pseudomonas infection			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

pulmonary sepsis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
respiratory tract infection			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
sepsis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	5 / 327 (1.53%)	4 / 329 (1.22%)	
occurrences causally related to treatment / all	0 / 7	0 / 5	
deaths causally related to treatment / all	0 / 2	0 / 1	
septic shock			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	3 / 327 (0.92%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 3	0 / 1	
staphylococcal infection			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
staphylococcal sepsis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
urinary tract infection			
alternative dictionary used: MedDRA 17.1			

subjects affected / exposed	1 / 327 (0.31%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
urinary tract infection bacterial			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
urosepsis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
viral infection			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
wound infection			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
cachexia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
decreased appetite			
alternative dictionary used: MedDRA 17.1			

subjects affected / exposed	2 / 327 (0.61%)	5 / 329 (1.52%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
dehydration			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	6 / 327 (1.83%)	6 / 329 (1.82%)	
occurrences causally related to treatment / all	0 / 7	0 / 7	
deaths causally related to treatment / all	0 / 1	0 / 0	
hypercalcaemia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypoalbuminaemia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	0 / 327 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
hyponatraemia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	3 / 327 (0.92%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypophagia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	1 / 327 (0.31%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This event is gender specific, only occurring in male or female subjects. The number of subjects exposed has been
adjusted accordingly.

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

Non-serious adverse events	Paclitaxel plus Ramucirumab	Paclitaxel plus Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	324 / 327 (99.08%)	321 / 329 (97.57%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
malignant neoplasm progression			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	15 / 327 (4.59%)	26 / 329 (7.90%)	
occurrences (all)	15	26	
Vascular disorders			
hypertension			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	80 / 327 (24.46%)	16 / 329 (4.86%)	
occurrences (all)	159	25	
General disorders and administration site conditions			
asthenia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	69 / 327 (21.10%)	44 / 329 (13.37%)	
occurrences (all)	186	72	
fatigue			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	128 / 327 (39.14%)	104 / 329 (31.61%)	
occurrences (all)	282	221	
oedema peripheral			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	81 / 327 (24.77%)	45 / 329 (13.68%)	
occurrences (all)	121	58	
pyrexia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	54 / 327 (16.51%)	35 / 329 (10.64%)	
occurrences (all)	81	53	
Respiratory, thoracic and mediastinal disorders			
cough			
alternative dictionary used: MedDRA 17.1			

subjects affected / exposed	42 / 327 (12.84%)	26 / 329 (7.90%)	
occurrences (all)	49	35	
dysphonia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	17 / 327 (5.20%)	9 / 329 (2.74%)	
occurrences (all)	22	13	
dyspnoea			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	42 / 327 (12.84%)	31 / 329 (9.42%)	
occurrences (all)	63	38	
epistaxis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	100 / 327 (30.58%)	23 / 329 (6.99%)	
occurrences (all)	157	34	
Psychiatric disorders			
insomnia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	31 / 327 (9.48%)	26 / 329 (7.90%)	
occurrences (all)	32	27	
Investigations			
alanine aminotransferase increased			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	21 / 327 (6.42%)	18 / 329 (5.47%)	
occurrences (all)	43	22	
aspartate aminotransferase increased			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	28 / 327 (8.56%)	17 / 329 (5.17%)	
occurrences (all)	63	23	
weight decreased			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	45 / 327 (13.76%)	49 / 329 (14.89%)	
occurrences (all)	81	69	
Nervous system disorders			

dizziness			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	20 / 327 (6.12%)	13 / 329 (3.95%)	
occurrences (all)	25	16	
dysgeusia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	29 / 327 (8.87%)	21 / 329 (6.38%)	
occurrences (all)	33	23	
headache			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	34 / 327 (10.40%)	22 / 329 (6.69%)	
occurrences (all)	52	37	
neuropathy peripheral			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	47 / 327 (14.37%)	30 / 329 (9.12%)	
occurrences (all)	88	51	
paraesthesia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	24 / 327 (7.34%)	25 / 329 (7.60%)	
occurrences (all)	42	41	
peripheral sensory neuropathy			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	57 / 327 (17.43%)	36 / 329 (10.94%)	
occurrences (all)	123	63	
polyneuropathy			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	18 / 327 (5.50%)	22 / 329 (6.69%)	
occurrences (all)	31	38	
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	111 / 327 (33.94%)	116 / 329 (35.26%)	
occurrences (all)	264	276	
leukopenia			
alternative dictionary used: MedDRA 17.1			

subjects affected / exposed	110 / 327 (33.64%)	69 / 329 (20.97%)	
occurrences (all)	470	201	
neutropenia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	173 / 327 (52.91%)	102 / 329 (31.00%)	
occurrences (all)	877	253	
thrombocytopenia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	41 / 327 (12.54%)	20 / 329 (6.08%)	
occurrences (all)	102	37	
Gastrointestinal disorders			
abdominal distension			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	22 / 327 (6.73%)	20 / 329 (6.08%)	
occurrences (all)	28	25	
abdominal pain			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	98 / 327 (29.97%)	61 / 329 (18.54%)	
occurrences (all)	165	103	
abdominal pain upper			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	34 / 327 (10.40%)	35 / 329 (10.64%)	
occurrences (all)	57	52	
ascites			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	31 / 327 (9.48%)	25 / 329 (7.60%)	
occurrences (all)	46	38	
constipation			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	71 / 327 (21.71%)	71 / 329 (21.58%)	
occurrences (all)	94	89	
diarrhoea			
alternative dictionary used: MedDRA 17.1			

subjects affected / exposed	103 / 327 (31.50%)	76 / 329 (23.10%)	
occurrences (all)	249	127	
dyspepsia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	17 / 327 (5.20%)	16 / 329 (4.86%)	
occurrences (all)	19	18	
dysphagia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	19 / 327 (5.81%)	17 / 329 (5.17%)	
occurrences (all)	28	18	
nausea			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	116 / 327 (35.47%)	106 / 329 (32.22%)	
occurrences (all)	238	183	
stomatitis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	64 / 327 (19.57%)	24 / 329 (7.29%)	
occurrences (all)	103	33	
vomiting			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	86 / 327 (26.30%)	65 / 329 (19.76%)	
occurrences (all)	142	111	
Skin and subcutaneous tissue disorders			
alopecia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	107 / 327 (32.72%)	127 / 329 (38.60%)	
occurrences (all)	137	159	
dry skin			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	25 / 327 (7.65%)	10 / 329 (3.04%)	
occurrences (all)	28	10	
pruritus			
alternative dictionary used: MedDRA 17.1			

subjects affected / exposed	21 / 327 (6.42%)	11 / 329 (3.34%)	
occurrences (all)	24	13	
rash			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	35 / 327 (10.70%)	25 / 329 (7.60%)	
occurrences (all)	44	28	
Renal and urinary disorders			
proteinuria			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	55 / 327 (16.82%)	20 / 329 (6.08%)	
occurrences (all)	158	35	
Musculoskeletal and connective tissue disorders			
arthralgia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	30 / 327 (9.17%)	20 / 329 (6.08%)	
occurrences (all)	55	25	
back pain			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	38 / 327 (11.62%)	39 / 329 (11.85%)	
occurrences (all)	48	47	
myalgia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	36 / 327 (11.01%)	32 / 329 (9.73%)	
occurrences (all)	64	44	
pain in extremity			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	20 / 327 (6.12%)	10 / 329 (3.04%)	
occurrences (all)	22	10	
Infections and infestations			
nasopharyngitis			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	23 / 327 (7.03%)	19 / 329 (5.78%)	
occurrences (all)	34	24	
urinary tract infection			
alternative dictionary used: MedDRA 17.1			

subjects affected / exposed	18 / 327 (5.50%)	11 / 329 (3.34%)	
occurrences (all)	22	11	
Metabolism and nutrition disorders			
decreased appetite			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	133 / 327 (40.67%)	105 / 329 (31.91%)	
occurrences (all)	230	172	
hypoalbuminaemia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	30 / 327 (9.17%)	13 / 329 (3.95%)	
occurrences (all)	46	16	
hyponatraemia			
alternative dictionary used: MedDRA 17.1			
subjects affected / exposed	17 / 327 (5.20%)	9 / 329 (2.74%)	
occurrences (all)	23	13	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 December 2010	Overall changes from version 1.1. included clarification of inclusion criteria 2, 4, 6, and 10 and clarifying the frequency of radiographic assessments and IDMC evaluations of safety data. Other additions centered on updates guidelines for ramucirumab administration regarding dose adjustments related to changes in body weight; paclitaxel administration; pharmacodynamic assessments; the management of proteinuria; and the removal of participants from ramucirumab/placebo in the instance of venous thrombotic events. (Safety Evaluations) was updated to reflect new Sponsor standards for the reporting of AEs and SAEs. (Treatment Requirements and Delays) was restructured and tables were added in order to provide additional clarification. Language was added regarding the chronic use of NSAIDs as well as additional information about planned subgroup analysis of the primary endpoint.
08 October 2012	Overall changes from version 2.0 included clarification of coagulation parameters in the inclusion/exclusion criteria; infusion times for study treatment; ramucirumab dose based on patient's body weight; complaint handling; and dose modifications of investigational drug in response to Grade 3 and Grade 4 AEs. Other additions included the additional information regarding CHF, impaired wound healing, liver injury/liver failure, and RPLS as AEs of concern; definitions of "study completion" and "extension period"; storage times for PK, pharmacodynamics, and immunogenicity blood samples; and ramucirumab discontinuation criteria related to liver injury/liver failure and CHF. The definition for "end of trial", premedication language, dose rationale, the timeframe of when survival follow-up would continue through, and the timeframe for blood collection for clinical laboratory tests prior to Days 1, 8, and 15 were updated.

Notes:

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.

One (1) participant was randomized to the placebo/paclitaxel group but received ramucirumab in error. For ITT population this participant was included in placebo/paclitaxel group and for the Safety population included in the ramucirumab group.

Notes: