



Clinical trial results:

A Phase 3, Randomized, Double-Blinded Study of IMC-1121B and Best Supportive Care (BSC) Versus Placebo and BSC in the Treatment of Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma Following Disease Progression on First-Line Platinum- or Fluoropyrimidine-Containing Combination Therapy

Summary

EudraCT number	2008-005964-15
Trial protocol	IT ES CZ MT GB
Global end of trial date	17 December 2015

Results information

Result version number	v1 (current)
This version publication date	24 December 2016
First version publication date	24 December 2016

Trial information

Trial identification

Sponsor protocol code	13893
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00917384
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Alias: I4T-IE-JVBD , Trial Number: 13893

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	17 December 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	17 December 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to gather information about the use of an investigational drug called Ramucirumab in adenocarcinomas of the stomach or gastroesophageal junction.

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	21 August 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 6
Country: Number of subjects enrolled	Australia: 12
Country: Number of subjects enrolled	Bosnia and Herzegovina: 4
Country: Number of subjects enrolled	Brazil: 38
Country: Number of subjects enrolled	Canada: 10
Country: Number of subjects enrolled	Chile: 2
Country: Number of subjects enrolled	Colombia: 3
Country: Number of subjects enrolled	Czech Republic: 37
Country: Number of subjects enrolled	Egypt: 1
Country: Number of subjects enrolled	Spain: 16
Country: Number of subjects enrolled	United Kingdom: 17
Country: Number of subjects enrolled	Guatemala: 8
Country: Number of subjects enrolled	Croatia: 7
Country: Number of subjects enrolled	Indonesia: 3
Country: Number of subjects enrolled	India: 24
Country: Number of subjects enrolled	Italy: 34
Country: Number of subjects enrolled	Korea, Republic of: 17
Country: Number of subjects enrolled	Lebanon: 1
Country: Number of subjects enrolled	Malta: 5
Country: Number of subjects enrolled	New Zealand: 2

Country: Number of subjects enrolled	Philippines: 2
Country: Number of subjects enrolled	Poland: 13
Country: Number of subjects enrolled	Romania: 17
Country: Number of subjects enrolled	Russian Federation: 22
Country: Number of subjects enrolled	Thailand: 1
Country: Number of subjects enrolled	Turkey: 6
Country: Number of subjects enrolled	Taiwan: 3
Country: Number of subjects enrolled	United States: 43
Country: Number of subjects enrolled	South Africa: 1
Worldwide total number of subjects	355
EEA total number of subjects	146

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)	224
From 65 to 84 years	129
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants who completed were those who died due to any cause or were alive and on study at conclusion but off treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	IMC-1121B (ramucirumab)

Arm description:

Participants received IMC-1121B (ramucirumab), administered via intravenous infusion every 2 weeks at a dose of 8 milligrams/kilogram (mg/kg), plus best supportive care (BSC) as determined appropriate by the investigator(s). Treatment continued until there was evidence of progressive disease (PD), the development of unacceptable toxicity, protocol noncompliance, or withdrawal of consent.

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

Dosage and administration details:

Participants received IMC-1121B (ramucirumab), administered via intravenous infusion every 2 weeks at a dose of 8 milligrams/kilogram (mg/kg), plus best supportive care (BSC).

Arm title	Placebo
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Arm description:

Participants received placebo by intravenous infusion every 2 weeks plus BSC as determined appropriate by the investigator(s). Because investigators and ancillary medical personnel were blinded as to assignment to active therapy versus placebo, the volume of placebo administered was calculated as if it were active product with a dose of 8 mg/kg. Treatment continued until there was evidence of PD, the development of unacceptable toxicity, protocol noncompliance, or withdrawal of consent.

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:

Participants received placebo by intravenous infusion every 2 weeks plus BSC.

Number of subjects in period 1	IMC-1121B (ramucirumab)	Placebo
Started	238	117
Received at least 1 dose of study drug	236	115
Completed	224	113
Not completed	14	4
Consent withdrawn by subject	10	2
Lost to follow-up	4	2

Baseline characteristics

Reporting groups

Reporting group title	IMC-1121B (ramucirumab)
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Reporting group description:

Participants received IMC-1121B (ramucirumab), administered via intravenous infusion every 2 weeks at a dose of 8 milligrams/kilogram (mg/kg), plus best supportive care (BSC) as determined appropriate by the investigator(s). Treatment continued until there was evidence of progressive disease (PD), the development of unacceptable toxicity, protocol noncompliance, or withdrawal of consent.

Reporting group title	Placebo
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Reporting group description:

Participants received placebo by intravenous infusion every 2 weeks plus BSC as determined appropriate by the investigator(s). Because investigators and ancillary medical personnel were blinded as to assignment to active therapy versus placebo, the volume of placebo administered was calculated as if it were active product with a dose of 8 mg/kg. Treatment continued until there was evidence of PD, the development of unacceptable toxicity, protocol noncompliance, or withdrawal of consent.

Reporting group values	IMC-1121B (ramucirumab)	Placebo	Total
Number of subjects	238	117	355
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	154	70	224
From 65-84 years	83	46	129
85 years and over	1	1	2
Gender, Male/Female Units: participants			
Female	69	38	107
Male	169	79	248
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	41	19	60
Not Hispanic or Latino	197	98	295
Unknown or Not Reported	0	0	0
Region of Enrollment Units: Subjects			
Argentina	4	2	6
Australia	8	4	12
Bosnia and Herzegovina	1	3	4
Brazil	24	14	38
Canada	8	2	10
Chile	1	1	2

Colombia	2	1	3
Czech Republic	24	13	37
Egypt	1	0	1
Spain	12	4	16
United Kingdom	13	4	17
Guatemala	6	2	8
Croatia	7	0	7
Indonesia	2	1	3
India	16	8	24
Italy	23	11	34
Korea, Republic of	11	6	17
Lebanon	1	0	1
Malta	2	3	5
New Zealand	1	1	2
Philippines	1	1	2
Poland	9	4	13
Romania	13	4	17
Russian Federation	14	8	22
Thailand	1	0	1
Turkey	5	1	6
Taiwan	3	0	3
United States	25	18	43
South Africa	0	1	1
Race			
Units: Subjects			
White	181	91	272
Asian	39	17	56
Black	4	2	6
Other	14	7	21

End points

End points reporting groups

Reporting group title	IMC-1121B (ramucirumab)
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Reporting group description:

Participants received IMC-1121B (ramucirumab), administered via intravenous infusion every 2 weeks at a dose of 8 milligrams/kilogram (mg/kg), plus best supportive care (BSC) as determined appropriate by the investigator(s). Treatment continued until there was evidence of progressive disease (PD), the development of unacceptable toxicity, protocol noncompliance, or withdrawal of consent.

Reporting group title	Placebo
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Reporting group description:

Participants received placebo by intravenous infusion every 2 weeks plus BSC as determined appropriate by the investigator(s). Because investigators and ancillary medical personnel were blinded as to assignment to active therapy versus placebo, the volume of placebo administered was calculated as if it were active product with a dose of 8 mg/kg. Treatment continued until there was evidence of PD, the development of unacceptable toxicity, protocol noncompliance, or withdrawal of consent.

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)
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End point description:

Overall survival is defined as the time from the date of randomization to the date of death from any cause. Participants who were alive at the date of data cut-off or who were lost to follow-up were censored on the last date the participant was known to be alive

End point type	Primary
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End point timeframe:

Randomization up to 28 months post-randomization

End point values	IMC-1121B (ramucirumab)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	238	117		
Units: months				
median (confidence interval 95%)	5.2 (4.4 to 5.7)	3.8 (2.8 to 4.7)		

Statistical analyses

Statistical analysis title	Overall Survival Statistical Analysis
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Comparison groups	IMC-1121B (ramucirumab) v Placebo
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Number of subjects included in analysis	355
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0473 ^[1]
Method	Stratified Log-Rank Test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.776
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.603
upper limit	0.998

Notes:

[1] - Stratified Log-Rank Test and HR stratified by randomization strata (weight loss over the prior 3 months, primary tumor site and geographical region).

Secondary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)
End point description:	
PFS is defined as the time from date of randomization until date of objectively determined progressive disease (PD) or death due to any cause, whichever is first. Participants alive and without PD were censored at the time of last adequate objective tumor assessment (that is, response other than unevaluable).	
End point type	Secondary
End point timeframe:	
Randomization up to 17 months	

End point values	IMC-1121B (ramucirumab)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	238	117		
Units: months				
median (confidence interval 95%)	2.1 (1.5 to 2.7)	1.3 (1.3 to 1.4)		

Statistical analyses

Statistical analysis title	Progression-Free Survival Statistical Analysis
Comparison groups	Placebo v IMC-1121B (ramucirumab)
Number of subjects included in analysis	355
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[2]
Method	Stratified Log-Rank Test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.483

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.376
upper limit	0.62

Notes:

[2] - Stratified Log-Rank Test and HR stratified by randomization strata (weight loss over the prior 3 months, primary tumor site and geographical region).

Secondary: Percentage of Participants Who are Progression-Free at Week 12 (PFS Rate)

End point title	Percentage of Participants Who are Progression-Free at Week 12 (PFS Rate)
End point description:	
The percentage of participants alive and progression-free 12 weeks after randomization. Progression-free survival (PFS) is defined as the time from the date of randomization until the date of objectively determined progressive disease (PD) or death due to any cause whichever comes first. Participants alive and without PD were censored at the time of the last adequate objective tumor assessment.	
End point type	Secondary
End point timeframe:	
Week 12 post-randomization	

End point values	IMC-1121B (ramucirumab)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	238	117		
Units: percentage of participants				
number (confidence interval 95%)	40.1 (33.6 to 46.4)	15.8 (9.7 to 23.3)		

Statistical analyses

Statistical analysis title	PFS Rate Statistical Analysis
Comparison groups	Placebo v IMC-1121B (ramucirumab)
Number of subjects included in analysis	355
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Normal Approximation
Parameter estimate	Difference Between Arms
Point estimate	24.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	14.9
upper limit	33.6

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

End point title	Percentage of Participants with Objective Response (Objective Response Rate [ORR])
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End point description:

ORR is equal to the percentage of participants achieving a best overall response of complete response (CR) or partial response (PR). CR and PR were defined using the Response Evaluation Criteria in Solid Tumors (RECIST v1.0). CR is defined as the disappearance of all target and non-target lesions, no appearance of new lesions and confirmed at the consecutive tumor assessment. PR is defined as at least a 30% decrease in the sum of the longest diameters (LD) of target lesions (taking as reference the baseline sum LD), no progression of non-target lesions, no appearance of new lesions and confirmed at a subsequent tumor assessment.

End point type	Secondary
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End point timeframe:

Randomization up to 17 months post-randomization

End point values	IMC-1121B (ramucirumab)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	238	117		
Units: percentage of participants				
number (confidence interval 95%)	3.4 (1.5 to 6.5)	2.6 (0.5 to 7.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)
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End point description:

DOR is the interval from date of initial documented response (complete response [CR] or partial response [PR]) to first documented date of disease progression (PD) or death as a result of any cause. CR and PR were defined using the Response Evaluation Criteria in Solid Tumors (RECIST v1.0). CR is defined as the disappearance of all target and non-target lesions, no appearance of new lesions and confirmed at the consecutive tumor assessment. PR is defined as at least a 30% decrease in the sum of the longest diameters (LD) of target lesions (taking as reference the baseline sum LD), no progression of non-target lesions, no appearance of new lesions and confirmed at a subsequent tumor assessment. Participants who did not relapse or die were censored at the time of the last adequate objective tumor assessment.

End point type	Secondary
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End point timeframe:

Randomization up to 17 months post-randomization

End point values	IMC-1121B (ramucirumab)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[3]	0 ^[4]		
Units: number				
number (not applicable)				

Notes:

[3] - The number of all responders (participants with CR or PR) was too small for a meaningful analysis.

[4] - The number of all responders (participants with CR or PR) was too small for a meaningful analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Quality of Life (QoL) as measured by the European Organisation for Research and Treatment of Cancer Questionnaire (EORTC-QLQ-C30)

End point title	Change from Baseline in Quality of Life (QoL) as measured by the European Organisation for Research and Treatment of Cancer Questionnaire (EORTC-QLQ-C30)
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End point description:

EORTC QLQ-C30 v3.0 is a self-administered questionnaire with multidimensional scales that measures 5 functional domains (physical, role, cognitive, emotional, and social), global health status, and symptom scales of fatigue, pain, nausea and vomiting, dyspnea, loss of appetite, insomnia, constipation and diarrhea, and financial difficulties. A linear transformation is applied to standardize the raw scores to range between 0 and 100 per developer guidelines. For functional domains and global health status, higher scores represent a better level of functioning. For symptoms scales, higher scores represented a greater degree of symptoms. Best change from baseline results determined by Least Square (LS) mean estimated with randomization stratification factors and baseline value as continuous covariate.

End point type	Secondary
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End point timeframe:

Baseline up to Cycle 10 (18 weeks [1 cycle=2 weeks])

End point values	IMC-1121B (ramucirumab)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114 ^[5]	26 ^[6]		
Units: units on a scale				
least squares mean (standard error)				
Global Health Status/QoL	2.42 (± 2.99)	0.8 (± 4.48)		
Physical Functioning	-6.26 (± 3.2)	-12.01 (± 4.82)		
Role Functioning	-4.32 (± 4.65)	-11.79 (± 6.99)		
Emotional Functioning	-1.61 (± 3.29)	-6.51 (± 4.92)		
Cognitive Functioning	-4.26 (± 2.63)	-10.94 (± 3.94)		
Social Functioning	-1.98 (± 3.9)	-1.37 (± 5.86)		
Fatigue	3.16 (± 3.43)	6.88 (± 5.16)		
Nausea and Vomiting	1.77 (± 2.86)	2.88 (± 4.32)		
Pain	0.13 (± 3.61)	3.85 (± 5.42)		
Dyspnea	-2.61 (± 3.35)	3.51 (± 5.08)		

Insomnia	-7.47 (± 4.19)	-3.95 (± 6.28)		
Appetite Loss	-1.01 (± 4.6)	7.16 (± 6.91)		
Constipation	0.09 (± 3.79)	7.94 (± 5.69)		
Diarrhea	-3.97 (± 1.64)	-5.49 (± 2.46)		
Financial Difficulties	-12.86 (± 3.78)	-2.39 (± 5.68)		

Notes:

[5] - All randomized participants with EORTC QLQ-C30 values at baseline and up to 18 weeks post-baseline.

[6] - All randomized participants with EORTC QLQ-C30 values at baseline and up to 18 weeks post-baseline.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events

End point title	Number of Participants with Adverse Events
End point description:	
Clinically significant events were defined as serious adverse events (SAE) and other treatment-emergent non-serious adverse events (NSAE). A summary of SAEs and all other NSAEs is located in the Reported Adverse Event module.	
End point type	Secondary
End point timeframe:	
Randomization up to 18 months	

End point values	IMC-1121B (ramucirumab)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	236 ^[7]	115 ^[8]		
Units: participants				
number (not applicable)				
Participants with SAE	112	51		
Participants with ≥ 1 treatment emergent NSAE	213	91		

Notes:

[7] - All randomized participants who received at least 1 dose of study drug.

[8] - All randomized participants who received at least 1 dose of study drug.

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum concentration (Cmax) of IMC-1121B

End point title	Maximum concentration (Cmax) of IMC-1121B
End point description:	
Cmax was not analyzed as only pre-dose samples were collected.	
End point type	Secondary
End point timeframe:	
6 weeks post-randomization	

End point values	IMC-1121B (ramucirumab)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[9]	0 ^[10]		
Units: number				
number (not applicable)				

Notes:

[9] - Cmax was not analyzed as only pre-dose samples were collected.

[10] - Cmax was not analyzed as only pre-dose samples were collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants who developed Antibodies against IMC-1121B

End point title	Number of Participants who developed Antibodies against IMC-1121B
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End point description:

The number of participants who developed treatment emergent antibody responses to IMC-1121B after baseline.

End point type	Secondary
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End point timeframe:

Baseline, 12 Weeks

End point values	IMC-1121B (ramucirumab)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207 ^[11]	106 ^[12]		
Units: participants				
number (not applicable)	6	1		

Notes:

[11] - Subset of the Safety Population: Received at least 1 dose of study drug and had immunogenicity data.

[12] - Subset of the Safety Population: Received at least 1 dose of study drug and had immunogenicity data.

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-JVBD

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	15.1
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Reporting groups

Reporting group title	Placebo + BSC
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Reporting group description: -

Reporting group title	Ramucirumab 8mg/kg + BSC
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Reporting group description: -

Serious adverse events	Placebo + BSC	Ramucirumab 8mg/kg + BSC	
Total subjects affected by serious adverse events			
subjects affected / exposed	51 / 115 (44.35%)	112 / 236 (47.46%)	
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)			
gastric cancer recurrent			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 115 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
gastric cancer			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 115 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
malignant pleural effusion			
alternative dictionary used: MedDRA 15.1			

subjects affected / exposed	0 / 115 (0.00%)	1 / 236 (0.42%)	
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 15.1			
subjects affected / exposed	3 / 115 (2.61%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
metastases to central nervous system alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	1 / 115 (0.87%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
metastases to spine alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 115 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
deep vein thrombosis alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	3 / 115 (2.61%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
embolism alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	1 / 115 (0.87%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypertension alternative dictionary used: MedDRA 15.1			

subjects affected / exposed	0 / 115 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypovolaemic shock			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 115 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
orthostatic hypotension			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 115 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
jejunostomy			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	1 / 115 (0.87%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
oesophageal stent insertion			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 115 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
asthenia			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	4 / 115 (3.48%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
chest pain			
alternative dictionary used: MedDRA 15.1			

subjects affected / exposed	0 / 115 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
death			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 115 (0.00%)	5 / 236 (2.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 5	
device dislocation			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	1 / 115 (0.87%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
disease progression			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	8 / 115 (6.96%)	10 / 236 (4.24%)	
occurrences causally related to treatment / all	1 / 8	1 / 10	
deaths causally related to treatment / all	0 / 6	1 / 8	
extravasation			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 115 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
fatigue			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	1 / 115 (0.87%)	2 / 236 (0.85%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
general physical health deterioration			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 115 (0.00%)	4 / 236 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 2	

mucosal inflammation alternative dictionary used: MedDRA 15.1 subjects affected / exposed	0 / 115 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
multi-organ failure alternative dictionary used: MedDRA 15.1 subjects affected / exposed	1 / 115 (0.87%)	6 / 236 (2.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 4	
pain alternative dictionary used: MedDRA 15.1 subjects affected / exposed	0 / 115 (0.00%)	2 / 236 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
pyrexia alternative dictionary used: MedDRA 15.1 subjects affected / exposed	1 / 115 (0.87%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
sudden death alternative dictionary used: MedDRA 15.1 subjects affected / exposed	1 / 115 (0.87%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
systemic inflammatory response syndrome alternative dictionary used: MedDRA 15.1 subjects affected / exposed	0 / 115 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders vaginal laceration alternative dictionary used:			

MedDRA 15.1			
subjects affected / exposed ^[1]	0 / 38 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
dyspnoea			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	2 / 115 (1.74%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
pleural effusion			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	1 / 115 (0.87%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pulmonary oedema			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 115 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pulmonary embolism			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	2 / 115 (1.74%)	2 / 236 (0.85%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	1 / 2	0 / 0	
respiratory failure			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	2 / 115 (1.74%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
Psychiatric disorders			
confusional state			
alternative dictionary used: MedDRA 15.1			

subjects affected / exposed	0 / 115 (0.00%)	1 / 236 (0.42%)	
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 15.1			
subjects affected / exposed	1 / 115 (0.87%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
aspartate aminotransferase increased			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 115 (0.00%)	2 / 236 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
alanine aminotransferase increased			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 115 (0.00%)	2 / 236 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
blood bilirubin increased			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 115 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
blood alkaline phosphatase increased			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 115 (0.00%)	4 / 236 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
weight decreased			
alternative dictionary used: MedDRA 15.1			

subjects affected / exposed	0 / 115 (0.00%)	1 / 236 (0.42%)	
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			
accidental overdose			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 115 (0.00%)	2 / 236 (0.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
drug dispensing error			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	1 / 115 (0.87%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
fall			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	2 / 115 (1.74%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
feeding tube complication			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	1 / 115 (0.87%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
incorrect dose administered			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	1 / 115 (0.87%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
medication error			
alternative dictionary used: MedDRA 15.1			

subjects affected / exposed	1 / 115 (0.87%)	7 / 236 (2.97%)	
occurrences causally related to treatment / all	0 / 2	3 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
multiple injuries			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 115 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
overdose			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 115 (0.00%)	2 / 236 (0.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
underdose			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	1 / 115 (0.87%)	4 / 236 (1.69%)	
occurrences causally related to treatment / all	1 / 1	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
cardiac arrest			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 115 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
myocardial infarction			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 115 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
sinus bradycardia			
alternative dictionary used: MedDRA 15.1			

subjects affected / exposed	1 / 115 (0.87%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
cerebral ischaemia			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 115 (0.00%)	1 / 236 (0.42%)	
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 15.1			
subjects affected / exposed	0 / 115 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
coma			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 115 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hyperammonaemic encephalopathy			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 115 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
headache			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 115 (0.00%)	1 / 236 (0.42%)	
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 15.1			

subjects affected / exposed	2 / 115 (1.74%)	11 / 236 (4.66%)	
occurrences causally related to treatment / all	0 / 4	1 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
disseminated intravascular coagulation			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 115 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
febrile neutropenia			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 115 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pancytopenia			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	2 / 115 (1.74%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
thrombocytopenia			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	2 / 115 (1.74%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
abdominal distension			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	1 / 115 (0.87%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
abdominal pain upper			
alternative dictionary used: MedDRA 15.1			

subjects affected / exposed	0 / 115 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
abdominal pain			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	3 / 115 (2.61%)	10 / 236 (4.24%)	
occurrences causally related to treatment / all	0 / 3	2 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
ascites			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	3 / 115 (2.61%)	6 / 236 (2.54%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
colonic obstruction			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	1 / 115 (0.87%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
constipation			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	2 / 115 (1.74%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
dyspepsia			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	1 / 115 (0.87%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
diarrhoea			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	2 / 115 (1.74%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

dysphagia			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	3 / 115 (2.61%)	6 / 236 (2.54%)	
occurrences causally related to treatment / all	1 / 4	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
haematemesis			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 115 (0.00%)	3 / 236 (1.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
gastrointestinal obstruction			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	1 / 115 (0.87%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
gastrointestinal haemorrhage			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	2 / 115 (1.74%)	2 / 236 (0.85%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
gastric haemorrhage			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	1 / 115 (0.87%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
ileus			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 115 (0.00%)	1 / 236 (0.42%)	
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 15.1			

subjects affected / exposed	0 / 115 (0.00%)	5 / 236 (2.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
intestinal perforation			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 115 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
large intestine perforation			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	1 / 115 (0.87%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	1 / 1	1 / 1	
obstruction gastric			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	1 / 115 (0.87%)	2 / 236 (0.85%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
nausea			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 115 (0.00%)	3 / 236 (1.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
oesophageal fistula			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	1 / 115 (0.87%)	0 / 236 (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 15.1			
subjects affected / exposed	0 / 115 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

oesophageal obstruction alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 115 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
proctalgia alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	1 / 115 (0.87%)	0 / 236 (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 15.1			
subjects affected / exposed	0 / 115 (0.00%)	2 / 236 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
upper gastrointestinal haemorrhage alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	1 / 115 (0.87%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
vomiting alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	5 / 115 (4.35%)	7 / 236 (2.97%)	
occurrences causally related to treatment / all	1 / 5	3 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
bile duct obstruction alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	1 / 115 (0.87%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
cholangitis alternative dictionary used: MedDRA 15.1			

subjects affected / exposed	1 / 115 (0.87%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
cholecystitis acute			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 115 (0.00%)	2 / 236 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
cholestasis			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 115 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
hyperbilirubinaemia			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	1 / 115 (0.87%)	0 / 236 (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 15.1			
subjects affected / exposed	0 / 115 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
liver disorder			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 115 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
nephrolithiasis			
alternative dictionary used: MedDRA 15.1			

subjects affected / exposed	0 / 115 (0.00%)	2 / 236 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
renal failure acute			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	2 / 115 (1.74%)	2 / 236 (0.85%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
ureteric obstruction			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 115 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
urinary tract obstruction			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 115 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
urinary retention			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	1 / 115 (0.87%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ureteric perforation			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 115 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
inappropriate antidiuretic hormone secretion			
alternative dictionary used: MedDRA 15.1			

subjects affected / exposed	0 / 115 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
back pain			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	1 / 115 (0.87%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
flank pain			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 115 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
abscess			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	1 / 115 (0.87%)	0 / 236 (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 15.1			
subjects affected / exposed	0 / 115 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
biliary sepsis			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 115 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
cystitis			
alternative dictionary used: MedDRA 15.1			

subjects affected / exposed	0 / 115 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
liver abscess			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	1 / 115 (0.87%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
lobar pneumonia			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	1 / 115 (0.87%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
lung infection			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	1 / 115 (0.87%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pneumonia			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	2 / 115 (1.74%)	4 / 236 (1.69%)	
occurrences causally related to treatment / all	0 / 2	1 / 4	
deaths causally related to treatment / all	0 / 0	1 / 2	
peritonitis			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 115 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pulmonary sepsis			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 115 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

sepsis alternative dictionary used: MedDRA 15.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	2 / 115 (1.74%) 1 / 2 0 / 0	3 / 236 (1.27%) 0 / 3 0 / 0	
respiratory tract infection alternative dictionary used: MedDRA 15.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 115 (0.00%) 0 / 0 0 / 0	1 / 236 (0.42%) 0 / 1 0 / 0	
septic shock alternative dictionary used: MedDRA 15.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 115 (0.87%) 0 / 1 0 / 1	0 / 236 (0.00%) 0 / 0 0 / 0	
Metabolism and nutrition disorders decreased appetite alternative dictionary used: MedDRA 15.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 115 (0.87%) 0 / 1 0 / 0	4 / 236 (1.69%) 2 / 4 0 / 0	
dehydration alternative dictionary used: MedDRA 15.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	3 / 115 (2.61%) 0 / 3 0 / 0	4 / 236 (1.69%) 2 / 4 0 / 1	
hyperkalaemia alternative dictionary used: MedDRA 15.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 115 (0.00%) 0 / 0 0 / 0	2 / 236 (0.85%) 0 / 7 0 / 0	
hypoalbuminaemia alternative dictionary used: MedDRA 15.1			

subjects affected / exposed	0 / 115 (0.00%)	3 / 236 (1.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypocalcaemia			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	1 / 115 (0.87%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypoglycaemia			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	2 / 115 (1.74%)	3 / 236 (1.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypokalaemia			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	1 / 115 (0.87%)	1 / 236 (0.42%)	
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 15.1			
subjects affected / exposed	0 / 115 (0.00%)	3 / 236 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypophagia			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	1 / 115 (0.87%)	0 / 236 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypoproteinaemia			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 115 (0.00%)	1 / 236 (0.42%)	
occurrences causally related to treatment / all	0 / 0	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: Number of participants adjusted for gender specific AE event.

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

Non-serious adverse events	Placebo + BSC	Ramucirumab 8mg/kg + BSC	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	91 / 115 (79.13%)	213 / 236 (90.25%)	
Investigations			
weight decreased			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	11 / 115 (9.57%)	26 / 236 (11.02%)	
occurrences (all)	13	34	
Vascular disorders			
hypertension			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	9 / 115 (7.83%)	35 / 236 (14.83%)	
occurrences (all)	31	125	
hypotension			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	6 / 115 (5.22%)	5 / 236 (2.12%)	
occurrences (all)	7	6	
Nervous system disorders			
dysgeusia			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	6 / 115 (5.22%)	7 / 236 (2.97%)	
occurrences (all)	9	7	
dizziness			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	6 / 115 (5.22%)	4 / 236 (1.69%)	
occurrences (all)	7	6	
headache			
alternative dictionary used: MedDRA 15.1			

subjects affected / exposed occurrences (all)	4 / 115 (3.48%) 4	21 / 236 (8.90%) 28	
Blood and lymphatic system disorders anaemia alternative dictionary used: MedDRA 15.1 subjects affected / exposed occurrences (all)	16 / 115 (13.91%) 22	33 / 236 (13.98%) 41	
General disorders and administration site conditions asthenia alternative dictionary used: MedDRA 15.1 subjects affected / exposed occurrences (all) fatigue alternative dictionary used: MedDRA 15.1 subjects affected / exposed occurrences (all) oedema peripheral alternative dictionary used: MedDRA 15.1 subjects affected / exposed occurrences (all)	16 / 115 (13.91%) 19 28 / 115 (24.35%) 52 10 / 115 (8.70%) 11	30 / 236 (12.71%) 60 58 / 236 (24.58%) 90 21 / 236 (8.90%) 27	
Gastrointestinal disorders abdominal pain alternative dictionary used: MedDRA 15.1 subjects affected / exposed occurrences (all) abdominal pain upper alternative dictionary used: MedDRA 15.1 subjects affected / exposed occurrences (all) constipation alternative dictionary used: MedDRA 15.1 subjects affected / exposed occurrences (all) diarrhoea alternative dictionary used: MedDRA 15.1	26 / 115 (22.61%) 36 5 / 115 (4.35%) 5 24 / 115 (20.87%) 38	40 / 236 (16.95%) 53 26 / 236 (11.02%) 35 37 / 236 (15.68%) 53	

subjects affected / exposed	9 / 115 (7.83%)	35 / 236 (14.83%)	
occurrences (all)	12	64	
ascites			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	8 / 115 (6.96%)	18 / 236 (7.63%)	
occurrences (all)	8	23	
dyspepsia			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	7 / 115 (6.09%)	6 / 236 (2.54%)	
occurrences (all)	7	8	
dysphagia			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	11 / 115 (9.57%)	23 / 236 (9.75%)	
occurrences (all)	22	33	
nausea			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	30 / 115 (26.09%)	45 / 236 (19.07%)	
occurrences (all)	44	62	
vomiting			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	26 / 115 (22.61%)	45 / 236 (19.07%)	
occurrences (all)	36	70	
Respiratory, thoracic and mediastinal disorders			
cough			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	9 / 115 (7.83%)	19 / 236 (8.05%)	
occurrences (all)	9	20	
epistaxis			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	1 / 115 (0.87%)	12 / 236 (5.08%)	
occurrences (all)	1	15	
dyspnoea			
alternative dictionary used: MedDRA 15.1			

subjects affected / exposed occurrences (all)	15 / 115 (13.04%) 23	21 / 236 (8.90%) 24	
Psychiatric disorders insomnia alternative dictionary used: MedDRA 15.1 subjects affected / exposed occurrences (all)	8 / 115 (6.96%) 8	13 / 236 (5.51%) 14	
Musculoskeletal and connective tissue disorders back pain alternative dictionary used: MedDRA 15.1 subjects affected / exposed occurrences (all) pain in extremity alternative dictionary used: MedDRA 15.1 subjects affected / exposed occurrences (all)	11 / 115 (9.57%) 22 6 / 115 (5.22%) 11	18 / 236 (7.63%) 22 8 / 236 (3.39%) 11	
Metabolism and nutrition disorders decreased appetite alternative dictionary used: MedDRA 15.1 subjects affected / exposed occurrences (all) hypoalbuminaemia alternative dictionary used: MedDRA 15.1 subjects affected / exposed occurrences (all) hypokalaemia alternative dictionary used: MedDRA 15.1 subjects affected / exposed occurrences (all)	26 / 115 (22.61%) 39 6 / 115 (5.22%) 6 5 / 115 (4.35%) 5	55 / 236 (23.31%) 90 11 / 236 (4.66%) 15 13 / 236 (5.51%) 20	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 July 2009	Version 4.0 - changes to Adverse Events (bleedings were added)
20 April 2010	Version 5.1 - included only minor changes/clarifications not affecting the conduct of the study / planned analyses.
23 November 2010	Version 6.0 - major changes - decrease in planned sample size; Study Duration and Extended Follow-Up/Survival ; Section on gastrointestinal perforation was added
31 October 2011	Version 7.0 - primary purpose was to increase the planned sample size to 348 patients from 315 patients; changed survival follow-up; create a clear definition of the end of the trial

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported