Clinical trial results:
Randomized Phase 2 Trial Evaluating Pharmacokinetics and Safety of Four Ramucirumab Dosing Regimens in Second-Line Gastric or Gastroesophageal Junction Adenocarcinoma

Summary

EudraCT number	2014-003791-23
Trial protocol	HU SK FR PL RO
Global end of trial date	05 June 2019

Results information

Result version number	v1 (current)
This version publication date	17 June 2020
First version publication date	17 June 2020

Trial information

Trial identification

Sponsor protocol code	I4T-MC-JVDB

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02443883
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Number: 15608

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 June 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 November 2016
Global end of trial reached?	Yes
Global end of trial date	05 June 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main purpose of this study was to evaluate the safety and pharmacokinetics of administering various dose regimens of ramucirumab in participants with advanced gastric cancer whose disease has progressed during or following prior chemotherapy.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 July 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	4 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Romania: 27
Country: Number of subjects enrolled	Turkey: 11
Country: Number of subjects enrolled	Hungary: 7
Country: Number of subjects enrolled	United States: 8
Country: Number of subjects enrolled	Poland: 24
Country: Number of subjects enrolled	United Kingdom: 31
Country: Number of subjects enrolled	Slovakia: 7
Country: Number of subjects enrolled	Australia: 8
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Russian Federation: 15
Country: Number of subjects enrolled	New Zealand: 7
Country: Number of subjects enrolled	Argentina: 14
Worldwide total number of subjects	164
EEA total number of subjects	101

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)	111
From 65 to 84 years	52
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Study completion was defined as death due to any cause or disease progression.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Ramucirumab Regimen 1

Arm description:

Ramucirumab (8milligram per kilogram [mg/kg]) given intravenously (IV) on day 1 and day 15 of each cycle (28-day cycle) until discontinuation criteria are met.

Arm type	Experimental
Investigational medicinal product name	8 mg/kg Ramucirumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ramucirumab (8milligram per kilogram [mg/kg]) given intravenously (IV) on day 1 and day 15 of each cycle (28-day cycle) until discontinuation criteria are met.

Arm title	Ramucirumab Regimen 2

Arm description:

Ramucirumab (12 mg/kg) given IV on day 1 and day 15 of each cycle (28-day cycle) until discontinuation criteria are met.

Arm type	Experimental
Investigational medicinal product name	12 mg/kg Ramucirumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ramucirumab (12 mg/kg) given IV on day 1 and day 15 of each cycle (28-day cycle) until discontinuation criteria are met.

Arm title	Ramucirumab Regimen 3

Arm description:

Ramucirumab (6 mg/kg) given IV on day 1, 8, 15 and 22 of each cycle (28-day cycle) until discontinuation criteria are met.

Arm type	Experimental

Investigational medicinal product name	6 mg/kg Ramucirumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ramucirumab (6 mg/kg) given IV on day 1, 8, 15 and 22 of each cycle (28-day cycle) until discontinuation criteria are met.

Arm title	Ramucirumab Regimen 4

Arm description:

Ramucirumab (8 mg/kg) given IV on day 1 and day 8 of each cycle (21-day cycle) until discontinuation criteria are met.

Arm type	Experimental
Investigational medicinal product name	8 mg/kg Ramucirumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ramucirumab (8 mg/kg) given IV on day 1 and day 8 of each cycle (21-day cycle) until discontinuation criteria are met.

Number of subjects in period 1	Ramucirumab Regimen 1	Ramucirumab Regimen 2	Ramucirumab Regimen 3
Started	40	42	41
Received at least one dose of study drug	38	42	41
Completed	34	38	40
Not completed	6	4	1
Consent withdrawn by subject	1	-	-
Physician decision	1	1	-
Adverse event, non-fatal	-	1	-
Lost to follow-up	3	2	1
Randomized, but never treated	1	-	-

Number of subjects in period 1	Ramucirumab Regimen 4
Started	41
Received at least one dose of study drug	40
Completed	36
Not completed	5
Consent withdrawn by subject	2
Physician decision	3
Adverse event, non-fatal	-
Lost to follow-up	-
Randomized, but never treated	-

Baseline characteristics

Reporting groups	
Reporting group title	Ramucirumab Regimen 1
Reporting group description:	
Ramucirumab (8milligram per kilogram [mg/kg]) given intravenously (IV) on day 1 and day 15 of each cycle (28-day cycle) until discontinuation criteria are met.	
Reporting group title	Ramucirumab Regimen 2
Reporting group description:	
Ramucirumab (12 mg/kg) given IV on day 1 and day 15 of each cycle (28-day cycle) until discontinuation criteria are met.	
Reporting group title	Ramucirumab Regimen 3
Reporting group description:	
Ramucirumab (6 mg/kg) given IV on day 1, 8, 15 and 22 of each cycle (28-day cycle) until discontinuation criteria are met.	
Reporting group title	Ramucirumab Regimen 4
Reporting group description:	
Ramucirumab (8 mg/kg) given IV on day 1 and day 8 of each cycle (21-day cycle) until discontinuation criteria are met.	

Reporting group values	Ramucirumab Regimen 1	Ramucirumab Regimen 2	Ramucirumab Regimen 3
Number of subjects	40	42	41
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	58.5	58.7	60.5
standard deviation	± 14.0	± 10.4	± 12.3
Gender categorical Units: Subjects			
Female	11	10	6
Male	29	32	35
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	6	3	6
Not Hispanic or Latino	32	37	33
Unknown or Not Reported	2	2	2
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	32	35	35
More than one race	6	7	5
Unknown or Not Reported	1	0	1
Region of Enrollment Units: Subjects			

New Zealand	2	1	1
Argentina	5	1	2
Romania	4	6	10
Turkey	3	4	2
Hungary	0	3	3
United States	2	3	2
Poland	6	6	7
United Kingdom	7	10	8
Slovakia	3	1	2
Australia	1	2	0
France	1	1	2
Russia	6	4	2

Reporting group values	Ramucirumab Regimen 4	Total	
Number of subjects	41	164	
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	56.2		
standard deviation	± 12.9	-	
Gender categorical Units: Subjects			
Female	9	36	
Male	32	128	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	7	22	
Not Hispanic or Latino	32	134	
Unknown or Not Reported	2	8	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	1	2	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	33	135	
More than one race	6	24	
Unknown or Not Reported	1	3	
Region of Enrollment Units: Subjects			
New Zealand	3	7	
Argentina	6	14	
Romania	7	27	
Turkey	2	11	
Hungary	1	7	
United States	1	8	
Poland	5	24	
United Kingdom	6	31	

Slovakia	1	7	
Australia	5	8	
France	1	5	
Russia	3	15	

End points

End points reporting groups

Reporting group title	Ramucirumab Regimen 1
Reporting group description:	
Ramucirumab (8milligram per kilogram [mg/kg]) given intravenously (IV) on day 1 and day 15 of each cycle (28-day cycle) until discontinuation criteria are met.	
Reporting group title	Ramucirumab Regimen 2
Reporting group description:	
Ramucirumab (12 mg/kg) given IV on day 1 and day 15 of each cycle (28-day cycle) until discontinuation criteria are met.	
Reporting group title	Ramucirumab Regimen 3
Reporting group description:	
Ramucirumab (6 mg/kg) given IV on day 1, 8, 15 and 22 of each cycle (28-day cycle) until discontinuation criteria are met.	
Reporting group title	Ramucirumab Regimen 4
Reporting group description:	
Ramucirumab (8 mg/kg) given IV on day 1 and day 8 of each cycle (21-day cycle) until discontinuation criteria are met.	

Primary: Pharmacokinetics (PK): Minimum Concentration (Cmin) of Ramucirumab

End point title	Pharmacokinetics (PK): Minimum Concentration (Cmin) of Ramucirumab[1]
End point description:	
The Cmin is the minimum observed serum concentration of ramucirumab. Analysis population description (APD) included all randomized participants who received at least one dose of ramucirumab and had evaluable ramucirumab PK data.	
End point type	Primary
End point timeframe:	
Day 29, 43, 71 and 85: predose	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No inferential statistics were planned or conducted for this endpoint.

End point values	Ramucirumab Regimen 1	Ramucirumab Regimen 2	Ramucirumab Regimen 3	Ramucirumab Regimen 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38[2]	42[3]	41[4]	40[5]
Units: microgram per milliliter (µg/mL)				
geometric mean (geometric coefficient of variation)				
Day 29	32.9 (± 51)	59.5 (± 60)	69.3 (± 45)	71.6 (± 37)
Day 43	47.6 (± 36)	71.0 (± 58)	83.0 (± 57)	57.4 (± 44)
Day 71	60.4 (± 34)	65.0 (± 60)	122 (± 65)	97.1 (± 46)
Day 85	64.3 (± 40)	79.4 (± 46)	125 (± 56)	81.6 (± 50)

Notes:

[2] - Day 29:n =29, Day 43:n = 15, Day 71:n = 6, Day 85: n = 6

[3] - Day 29:n =32, Day 43:n = 22, Day 71:n = 12, Day 85: n = 10

[4] - Day 29:n =28, Day 43:n = 18, Day 71:n = 12, Day 85: n = 11

[5] - Day 29:n =31, Day 43:n = 17, Day 71:n = 10, Day 85: n = 9

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity: Number of Participants with Anti-Ramucirumab Antibodies

End point title	Immunogenicity: Number of Participants with Anti-Ramucirumab Antibodies

End point description:

Number of participants with positive treatment emergent anti-ramucirumab antibodies was summarized by treatment group. A treatment-emergent anti-drug antibodies (TEADA) sample was defined as: a post treatment sample with at least a 4-fold increase in titer from pre treatment sample; or 1:20 post treatment titer for participants that had no detectable ADA titer at baseline. APD included all randomized participants who received at least 1 dose of ramucirumab and had evaluable anti-ramucirumab antibody measurement.

End point type	Secondary

End point timeframe:

Predose Cycle 1 Through Short Term Follow Up (Up to 5 Months)

End point values	Ramucirumab Regimen 1	Ramucirumab Regimen 2	Ramucirumab Regimen 3	Ramucirumab Regimen 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19	26	20	22
Units: Participants				
number (not applicable)	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Progression Free Survival (PFS) at the First 6-Week Tumor Assessment

End point title	Rate of Progression Free Survival (PFS) at the First 6-Week Tumor Assessment

End point description:

PFS defined as the time from first day of therapy to first evidence of disease progression per RECIST v1.1 or death from any cause up to the first 6-week tumor assessment. Progressive Disease (PD) is at least 20% increase in sum of diameters of target lesions,taking as reference smallest sum on study and absolute increase of at least 5 mm.Appearance of 1 or more new lesions was also considered progression. Nontarget PD is unequivocal progression of existing nontarget lesions.Appearance of 1 or more new nontarget lesions was also considered PD.Participants with no baseline disease assessment: PFS time was censored at the randomization date,regardless of whether or not objectively determined disease progression or death has been observed.APD included randomized participants. Censored participants:Ramucirumab Regimen 1=8,Ramucirumab Regimen 2=10,Ramucirumab Regimen 3=8 and Ramucirumab Regimen 4=12. PFS rate at the first 6- week assessments was estimated using the Kaplan-Meir method.

End point type	Secondary

End point timeframe:

Baseline until the first 6-week tumor assessment

End point values	Ramucirumab Regimen 1	Ramucirumab Regimen 2	Ramucirumab Regimen 3	Ramucirumab Regimen 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40	42	41	41
Units: Months				
median (confidence interval 95%)	43.9 (27.3 to 59.3)	61.9 (44.9 to 75.0)	53.0 (36.2 to 67.3)	51.2 (34.2 to 65.9)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up To 4 Years	
Adverse event reporting additional description:	
All randomized participants who received at least one dose of study drug.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups	
Reporting group title	Ramucirumab Regimen 1
Reporting group description:	
Ramucirumab (8 mg/kg) given IV on day 1 and day 15 of each cycle (28-day cycle) until discontinuation criteria are met.	
Reporting group title	Ramucirumab Regimen 2
Reporting group description:	
Ramucirumab (12 mg/kg) given IV on day 1 and day 15 of each cycle (28-day cycle) until discontinuation criteria are met.	
Reporting group title	Ramucirumab Regimen 3
Reporting group description:	
Ramucirumab (6 mg/kg) given IV on day 1, 8, 15 and 22 of each cycle (28-day cycle) until discontinuation criteria are met.	
Reporting group title	Ramucirumab Regimen 4
Reporting group description:	
Ramucirumab (8 mg/kg) given IV on day 1 and day 8 of each cycle (21-day cycle) until discontinuation criteria are met.	

Serious adverse events	Ramucirumab Regimen 1	Ramucirumab Regimen 2	Ramucirumab Regimen 3
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 38 (26.32%)	11 / 42 (26.19%)	10 / 41 (24.39%)
number of deaths (all causes)	1	2	7
number of deaths resulting from adverse events	0	1	5
Surgical and medical procedures			
thoracic cavity drainage			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 38 (0.00%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
asthenia			
alternative dictionary used: MedDRA 22.1			

subjects affected / exposed	0 / 38 (0.00%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
chest pain			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 38 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
fatigue			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 38 (0.00%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
non-cardiac chest pain			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	2 / 38 (5.26%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pain			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 38 (2.63%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pyrexia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	2 / 38 (5.26%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
sudden death			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 38 (0.00%)	0 / 42 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Respiratory, thoracic and mediastinal disorders			
dyspnoea			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 38 (0.00%)	1 / 42 (2.38%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
haemoptysis			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 38 (0.00%)	0 / 42 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
pleural effusion			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 38 (0.00%)	0 / 42 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pneumothorax			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 38 (2.63%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pulmonary embolism			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 38 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
respiratory failure			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 38 (0.00%)	0 / 42 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Investigations			
blood creatinine increased			

alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 38 (2.63%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
overdose			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 38 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
procedural nausea			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 38 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
procedural vomiting			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 38 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
cardiac arrest			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 38 (2.63%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
cardiac failure congestive			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 38 (0.00%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
myocardial infarction			
alternative dictionary used: MedDRA 22.1			

subjects affected / exposed	0 / 38 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
syncope			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 38 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 38 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
abdominal pain			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 38 (2.63%)	2 / 42 (4.76%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
abdominal pain upper			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 38 (0.00%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ascites			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 38 (0.00%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
constipation			
alternative dictionary used: MedDRA 22.1			

subjects affected / exposed	0 / 38 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
diarrhoea			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 38 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
duodenal ulcer haemorrhage			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 38 (2.63%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
dysphagia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 38 (0.00%)	1 / 42 (2.38%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
gastric haemorrhage			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 38 (0.00%)	0 / 42 (0.00%)	3 / 41 (7.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 2
gastric perforation			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 38 (2.63%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
gastrointestinal haemorrhage			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 38 (0.00%)	0 / 42 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

haematemesis			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 38 (0.00%)	0 / 42 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
intestinal perforation			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 38 (0.00%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
nausea			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 38 (0.00%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
oesophageal perforation			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 38 (2.63%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
oesophageal spasm			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 38 (2.63%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
upper gastrointestinal haemorrhage			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 38 (0.00%)	1 / 42 (2.38%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
vomiting			
alternative dictionary used: MedDRA 22.1			

subjects affected / exposed	1 / 38 (2.63%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
cholangitis			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 38 (0.00%)	0 / 42 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hepatic failure			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 38 (0.00%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
acute kidney injury			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 38 (0.00%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
back pain			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 38 (2.63%)	0 / 42 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
bone pain			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 38 (0.00%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
biliary sepsis			
alternative dictionary used: MedDRA 22.1			

subjects affected / exposed	0 / 38 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
device related infection			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 38 (2.63%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
lower respiratory tract infection			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 38 (0.00%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pneumonia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 38 (0.00%)	2 / 42 (4.76%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
sepsis			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 38 (0.00%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
upper respiratory tract infection			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 38 (0.00%)	0 / 42 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
hyperkalaemia			
alternative dictionary used: MedDRA 22.1			

subjects affected / exposed	0 / 38 (0.00%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Ramucirumab Regimen 4		
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 40 (45.00%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	0		
Surgical and medical procedures			
thoracic cavity drainage			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
asthenia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
chest pain			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
fatigue			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
non-cardiac chest pain			
alternative dictionary used: MedDRA 22.1			

subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
pain				
alternative dictionary used: MedDRA 22.1				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
pyrexia				
alternative dictionary used: MedDRA 22.1				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
sudden death				
alternative dictionary used: MedDRA 22.1				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
dyspnoea				
alternative dictionary used: MedDRA 22.1				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
haemoptysis				
alternative dictionary used: MedDRA 22.1				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
pleural effusion				
alternative dictionary used: MedDRA 22.1				

subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
pneumothorax				
alternative dictionary used: MedDRA 22.1				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
pulmonary embolism				
alternative dictionary used: MedDRA 22.1				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
respiratory failure				
alternative dictionary used: MedDRA 22.1				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Investigations				
blood creatinine increased				
alternative dictionary used: MedDRA 22.1				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
overdose				
alternative dictionary used: MedDRA 22.1				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
procedural nausea				
alternative dictionary used: MedDRA 22.1				

subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
procedural vomiting			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
cardiac arrest			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
cardiac failure congestive			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
myocardial infarction			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
syncope			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 22.1			

subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
abdominal pain			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
abdominal pain upper			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
ascites			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
constipation			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
diarrhoea			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
duodenal ulcer haemorrhage			
alternative dictionary used: MedDRA 22.1			

subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
dysphagia				
alternative dictionary used: MedDRA 22.1				
subjects affected / exposed	2 / 40 (5.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
gastric haemorrhage				
alternative dictionary used: MedDRA 22.1				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
gastric perforation				
alternative dictionary used: MedDRA 22.1				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
gastrointestinal haemorrhage				
alternative dictionary used: MedDRA 22.1				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
haematemesis				
alternative dictionary used: MedDRA 22.1				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
intestinal perforation				
alternative dictionary used: MedDRA 22.1				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			

nausea				
alternative dictionary used: MedDRA 22.1				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
oesophageal perforation				
alternative dictionary used: MedDRA 22.1				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
oesophageal spasm				
alternative dictionary used: MedDRA 22.1				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
upper gastrointestinal haemorrhage				
alternative dictionary used: MedDRA 22.1				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
vomiting				
alternative dictionary used: MedDRA 22.1				
subjects affected / exposed	4 / 40 (10.00%)			
occurrences causally related to treatment / all	1 / 5			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
cholangitis				
alternative dictionary used: MedDRA 22.1				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
hepatic failure				
alternative dictionary used: MedDRA 22.1				

subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Renal and urinary disorders			
acute kidney injury			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
back pain			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
bone pain			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
biliary sepsis			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
device related infection			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
lower respiratory tract infection			
alternative dictionary used: MedDRA 22.1			

subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
pneumonia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
sepsis			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
upper respiratory tract infection			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
hyperkalaemia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Ramucirumab Regimen 1	Ramucirumab Regimen 2	Ramucirumab Regimen 3
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 38 (78.95%)	31 / 42 (73.81%)	36 / 41 (87.80%)
Vascular disorders			
hypertension			
alternative dictionary used: MedDRA 22.1			

subjects affected / exposed	6 / 38 (15.79%)	2 / 42 (4.76%)	7 / 41 (17.07%)
occurrences (all)	8	3	8
General disorders and administration site conditions			
asthenia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	2 / 38 (5.26%)	3 / 42 (7.14%)	4 / 41 (9.76%)
occurrences (all)	2	3	8
early satiety			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 38 (0.00%)	3 / 42 (7.14%)	0 / 41 (0.00%)
occurrences (all)	0	6	0
fatigue			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	10 / 38 (26.32%)	12 / 42 (28.57%)	6 / 41 (14.63%)
occurrences (all)	12	17	7
oedema peripheral			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 38 (2.63%)	4 / 42 (9.52%)	2 / 41 (4.88%)
occurrences (all)	1	5	2
pyrexia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	4 / 38 (10.53%)	2 / 42 (4.76%)	4 / 41 (9.76%)
occurrences (all)	4	2	5
Respiratory, thoracic and mediastinal disorders			
cough			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	2 / 38 (5.26%)	3 / 42 (7.14%)	1 / 41 (2.44%)
occurrences (all)	4	6	1
dyspnoea			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	4 / 38 (10.53%)	3 / 42 (7.14%)	1 / 41 (2.44%)
occurrences (all)	5	4	1
epistaxis			
alternative dictionary used: MedDRA 22.1			

subjects affected / exposed	1 / 38 (2.63%)	2 / 42 (4.76%)	6 / 41 (14.63%)
occurrences (all)	1	3	7
pleural effusion			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	2 / 38 (5.26%)	0 / 42 (0.00%)	1 / 41 (2.44%)
occurrences (all)	2	0	1
Psychiatric disorders			
insomnia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 38 (2.63%)	3 / 42 (7.14%)	2 / 41 (4.88%)
occurrences (all)	1	3	2
Investigations			
alanine aminotransferase increased			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	3 / 38 (7.89%)	5 / 42 (11.90%)	0 / 41 (0.00%)
occurrences (all)	3	7	0
aspartate aminotransferase increased			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	6 / 38 (15.79%)	5 / 42 (11.90%)	3 / 41 (7.32%)
occurrences (all)	6	8	3
blood alkaline phosphatase increased			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	4 / 38 (10.53%)	5 / 42 (11.90%)	2 / 41 (4.88%)
occurrences (all)	4	5	2
blood bilirubin increased			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	3 / 38 (7.89%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences (all)	3	0	0
weight decreased			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	3 / 38 (7.89%)	2 / 42 (4.76%)	3 / 41 (7.32%)
occurrences (all)	4	2	3
Injury, poisoning and procedural complications			

infusion related reaction			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	2 / 38 (5.26%)	0 / 42 (0.00%)	2 / 41 (4.88%)
occurrences (all)	2	0	2
Nervous system disorders			
headache			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	4 / 38 (10.53%)	6 / 42 (14.29%)	5 / 41 (12.20%)
occurrences (all)	8	8	8
lethargy			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	2 / 38 (5.26%)	1 / 42 (2.38%)	1 / 41 (2.44%)
occurrences (all)	2	1	1
paraesthesia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	2 / 38 (5.26%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences (all)	2	1	0
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	4 / 38 (10.53%)	5 / 42 (11.90%)	5 / 41 (12.20%)
occurrences (all)	12	15	11
Gastrointestinal disorders			
abdominal distension			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 38 (0.00%)	1 / 42 (2.38%)	1 / 41 (2.44%)
occurrences (all)	0	1	1
abdominal pain			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	6 / 38 (15.79%)	10 / 42 (23.81%)	7 / 41 (17.07%)
occurrences (all)	7	14	9
constipation			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	2 / 38 (5.26%)	5 / 42 (11.90%)	7 / 41 (17.07%)
occurrences (all)	2	8	7
diarrhoea			

alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	3 / 38 (7.89%)	9 / 42 (21.43%)	4 / 41 (9.76%)
occurrences (all)	4	12	5
dyspepsia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 38 (0.00%)	1 / 42 (2.38%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
dysphagia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 38 (2.63%)	3 / 42 (7.14%)	2 / 41 (4.88%)
occurrences (all)	1	9	2
nausea			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	6 / 38 (15.79%)	4 / 42 (9.52%)	4 / 41 (9.76%)
occurrences (all)	7	4	5
vomiting			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	6 / 38 (15.79%)	6 / 42 (14.29%)	8 / 41 (19.51%)
occurrences (all)	8	7	13
Skin and subcutaneous tissue disorders			
pruritus			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	2 / 38 (5.26%)	1 / 42 (2.38%)	2 / 41 (4.88%)
occurrences (all)	3	2	2
Renal and urinary disorders			
proteinuria			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	4 / 38 (10.53%)	1 / 42 (2.38%)	2 / 41 (4.88%)
occurrences (all)	5	1	3
Musculoskeletal and connective tissue disorders			
back pain			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	2 / 38 (5.26%)	3 / 42 (7.14%)	1 / 41 (2.44%)
occurrences (all)	5	5	2
muscular weakness			

alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	3 / 38 (7.89%)	1 / 42 (2.38%)	2 / 41 (4.88%)
occurrences (all)	4	1	3
Infections and infestations			
nasopharyngitis			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	2 / 38 (5.26%)	0 / 42 (0.00%)	0 / 41 (0.00%)
occurrences (all)	2	0	0
Metabolism and nutrition disorders			
decreased appetite			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	8 / 38 (21.05%)	9 / 42 (21.43%)	11 / 41 (26.83%)
occurrences (all)	11	16	13
dehydration			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	2 / 38 (5.26%)	1 / 42 (2.38%)	1 / 41 (2.44%)
occurrences (all)	3	4	2
hypoalbuminaemia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	4 / 38 (10.53%)	2 / 42 (4.76%)	3 / 41 (7.32%)
occurrences (all)	5	2	4
hyponatraemia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	3 / 38 (7.89%)	1 / 42 (2.38%)	2 / 41 (4.88%)
occurrences (all)	3	1	3

Non-serious adverse events	Ramucirumab Regimen 4		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 40 (77.50%)		
Vascular disorders			
hypertension			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	6 / 40 (15.00%)		
occurrences (all)	10		
General disorders and administration site conditions			

asthenia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	4		
early satiety			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
fatigue			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	9 / 40 (22.50%)		
occurrences (all)	9		
oedema peripheral			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	3		
pyrexia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
cough			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
dyspnoea			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	4 / 40 (10.00%)		
occurrences (all)	4		
epistaxis			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
pleural effusion			
alternative dictionary used:			

MedDRA 22.1 subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		
Psychiatric disorders insomnia alternative dictionary used: MedDRA 22.1 subjects affected / exposed occurrences (all)	 2 / 40 (5.00%) 2		
Investigations alanine aminotransferase increased alternative dictionary used: MedDRA 22.1 subjects affected / exposed occurrences (all) aspartate aminotransferase increased alternative dictionary used: MedDRA 22.1 subjects affected / exposed occurrences (all) blood alkaline phosphatase increased alternative dictionary used: MedDRA 22.1 subjects affected / exposed occurrences (all) blood bilirubin increased alternative dictionary used: MedDRA 22.1 subjects affected / exposed occurrences (all) weight decreased alternative dictionary used: MedDRA 22.1 subjects affected / exposed occurrences (all)	 1 / 40 (2.50%) 1 1 / 40 (2.50%) 1 1 / 40 (2.50%) 1 0 / 40 (0.00%) 0 2 / 40 (5.00%) 2		
Injury, poisoning and procedural complications infusion related reaction alternative dictionary used: MedDRA 22.1 subjects affected / exposed occurrences (all)	 0 / 40 (0.00%) 0		
Nervous system disorders			

headache			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		
lethargy			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
paraesthesia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Gastrointestinal disorders			
abdominal distension			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		
abdominal pain			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	4 / 40 (10.00%)		
occurrences (all)	8		
constipation			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	7 / 40 (17.50%)		
occurrences (all)	7		
diarrhoea			
alternative dictionary used: MedDRA 22.1			
subjects affected / exposed	5 / 40 (12.50%)		
occurrences (all)	5		
dyspepsia			

alternative dictionary used: MedDRA 22.1 subjects affected / exposed occurrences (all) dysphagia alternative dictionary used: MedDRA 22.1 subjects affected / exposed occurrences (all) nausea alternative dictionary used: MedDRA 22.1 subjects affected / exposed occurrences (all) vomiting alternative dictionary used: MedDRA 22.1 subjects affected / exposed occurrences (all)	4 / 40 (10.00%) 4 2 / 40 (5.00%) 2 7 / 40 (17.50%) 9 7 / 40 (17.50%) 10		
Skin and subcutaneous tissue disorders pruritus alternative dictionary used: MedDRA 22.1 subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		
Renal and urinary disorders proteinuria alternative dictionary used: MedDRA 22.1 subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2		
Musculoskeletal and connective tissue disorders back pain alternative dictionary used: MedDRA 22.1 subjects affected / exposed occurrences (all) muscular weakness alternative dictionary used: MedDRA 22.1 subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2 0 / 40 (0.00%) 0		
Infections and infestations			

nasopharyngitis alternative dictionary used: MedDRA 22.1 subjects affected / exposed occurrences (all)	 0 / 40 (0.00%) 0		
Metabolism and nutrition disorders decreased appetite alternative dictionary used: MedDRA 22.1 subjects affected / exposed occurrences (all)	 7 / 40 (17.50%) 8		
dehydration alternative dictionary used: MedDRA 22.1 subjects affected / exposed occurrences (all)	 4 / 40 (10.00%) 6		
hypoalbuminaemia alternative dictionary used: MedDRA 22.1 subjects affected / exposed occurrences (all)	 0 / 40 (0.00%) 0		
hyponatraemia alternative dictionary used: MedDRA 22.1 subjects affected / exposed occurrences (all)	 1 / 40 (2.50%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 April 2015	1. Inclusion and exclusion criteria regarding the use of anti coagulation therapy were amended; 2. Dose Modification, and its subsections, criteria for administration of ramucirumab to patients with hypertension were amended to align with other studies of ramucirumab in gastric cancer; 3. Safety monitoring, instructions for when to initiate monitoring of hepatic function were amended to align with lilly policy. 4. Short-Term and long term follow-up visits are modified.
11 December 2015	Revises the study's inclusion criteria to allow enrollment of patients who were previously treated with taxanes.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported