Clinical trial results:
Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Ramucirumab and Best Supportive Care (BSC) Versus Placebo and BSC as Second-Line Treatment in Patients With Hepatocellular Carcinoma and Elevated Baseline Alpha-Fetoprotein (AFP) Following First-Line Therapy With Sorafenib

Summary

EudraCT number	2014-005068-13
Trial protocol	DE ES AT CZ PL BE FR IT
Global end of trial date	19 November 2021

Results information

Result version number	v1 (current)
This version publication date	15 December 2022
First version publication date	15 December 2022

Trial information

Trial identification

Sponsor protocol code	I4T-MC-JVDE

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02435433
WHO universal trial number (UTN)	U1111-1165-1891
Other trial identifiers	Trial Number: 15755

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	19 November 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 November 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate the safety and efficacy of ramucirumab in participants with hepatocellular carcinoma (HCC) and elevated baseline alpha-fetoprotein. Participants will be randomized to ramucirumab or placebo in a 2:1 ratio (Main Global Cohort and China Maximized Extended Enrollment [MEE] Cohort). Participants may also receive ramucirumab if eligible to be enrolled in Open-Label Expansion (OLE) Cohort.

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	20 July 2015
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	Hong Kong: 22
Country: Number of subjects enrolled	United States: 23
Country: Number of subjects enrolled	Czechia: 6
Country: Number of subjects enrolled	Japan: 59
Country: Number of subjects enrolled	United Kingdom: 11
Country: Number of subjects enrolled	Switzerland: 5
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Korea, Republic of: 38
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	China: 76
Country: Number of subjects enrolled	Taiwan: 76
Country: Number of subjects enrolled	Brazil: 9
Country: Number of subjects enrolled	Poland: 5
Country: Number of subjects enrolled	Italy: 22
Country: Number of subjects enrolled	Israel: 1
Country: Number of subjects enrolled	Australia: 3

Country: Number of subjects enrolled	France: 51
Country: Number of subjects enrolled	Germany: 23
Worldwide total number of subjects	443
EEA total number of subjects	118

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)	266
From 65 to 84 years	174
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

. Main study: Participants who received sorafenib as first-line therapy were randomized to ramucirumab or placebo.
. OLE: Participants who were not previously treated with sorafenib were enrolled into this single-arm addenda and treated with ramucirumab to monitor safety.
. China MEE: This is an extension phase of the main study to monitor safety

Pre-assignment

Screening details:

- The actual enrollment in the study was 399 participants, as mentioned in the protocol section. However, the count here is 443 due to the overlapping of 44 participants who participated in the main study as well as the China MEE.
- Completers include participants who died due to any cause or alive, at the end of study, 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

Arms

Are arms mutually exclusive?	Yes
Arm title	Ramucirumab + BSC

Arm description:

8 milligrams per kilogram (mg/kg) ramucirumab administered as an intravenous (IV) injection on day 1 of each 14-day cycle. Participants may continue treatment until discontinuation criteria are met.

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

Dosage and administration details:

Administered IV

Arm title	Placebo + BSC

Arm description:

Placebo administered IV on day 1 of each 14 day cycle. Participants may continue treatment until discontinuation criteria are met.

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

Dosage and administration details:

Administered IV

Arm title	Open Label Ramucirumab + BSC

Arm description:

8 mg/kg ramucirumab administered IV on day 1 of each 14 day cycle. Participants may continue treatment until discontinuation criteria are met.

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

Dosage and administration details:

Administered IV

Arm title	Ramucirumab MEE Cohort

Arm description:

8 mg/kg ramucirumab administered IV on day 1 of each 14-day cycle. Participants may continue treatment until discontinuation criteria are met.

Number of participants: 31 (main study) + 39 (new enrolment)

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

Dosage and administration details:

Administered IV

Arm title	Placebo MEE Cohort

Arm description:

Placebo administered IV on day 1 of each 14-day cycle. Participants may continue treatment until discontinuation criteria are met.

Number of participants: 13 (main study) + 21 (new enrolment)

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

Dosage and administration details:

Administered IV

Number of subjects in period 1	Ramucirumab + BSC	Placebo + BSC	Open Label Ramucirumab + BSC
Started	197	95	47
Participants who received study drug	197	95	47
Completed	193	90	42
Not completed	4	5	5
Consent withdrawn by subject	2	3	1
Lost to follow-up	2	2	4

Number of subjects in period 1	Ramucirumab MEE Cohort	Placebo MEE Cohort
Started	70	34
Participants who received study drug	70	34
Completed	69	33
Not completed	1	1
Consent withdrawn by subject	-	1
Lost to follow-up	1	-

Baseline characteristics

Reporting groups

Reporting group title	Ramucirumab + BSC

Reporting group description:

8 milligrams per kilogram (mg/kg) ramucirumab administered as an intravenous (IV) injection on day 1 of each 14-day cycle. Participants may continue treatment until discontinuation criteria are met.

Reporting group title	Placebo + BSC

Reporting group description:

Placebo administered IV on day 1 of each 14 day cycle. Participants may continue treatment until discontinuation criteria are met.

Reporting group title	Open Label Ramucirumab + BSC

Reporting group description:

8 mg/kg ramucirumab administered IV on day 1 of each 14 day cycle. Participants may continue treatment until discontinuation criteria are met.

Reporting group title	Ramucirumab MEE Cohort

Reporting group description:

8 mg/kg ramucirumab administered IV on day 1 of each 14-day cycle. Participants may continue treatment until discontinuation criteria are met.

Number of participants: 31 (main study) + 39 (new enrolment)

Reporting group title	Placebo MEE Cohort

Reporting group description:

Placebo administered IV on day 1 of each 14-day cycle. Participants may continue treatment until discontinuation criteria are met.

Number of participants: 13 (main study) + 21 (new enrolment)

Reporting group values	Ramucirumab + BSC	Placebo + BSC	Open Label Ramucirumab + BSC
Number of subjects	197	95	47
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
median	64	64	61
full range (min-max)	30 to 88	26 to 85	36 to 82
Gender categorical Units: Subjects			
Female	43	16	6
Male	154	79	41

Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	12	9	1
Not Hispanic or Latino	129	58	40
Unknown or Not Reported	56	28	6
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	102	45	26
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	1	4
White	60	31	13
More than one race	0	1	4
Unknown or Not Reported	34	17	0
Region of Enrollment Units: Subjects			
Hong Kong	6	1	8
United States	10	1	12
Czechia	4	2	0
Japan	41	18	0
United Kingdom	9	2	0
Switzerland	2	2	1
Spain	3	2	0
Canada	1	1	0
Austria	1	1	0
South Korea	24	14	0
Belgium	2	2	0
China	3	1	8
Taiwan	22	11	10
Brazil	5	4	0
Poland	2	3	0
Italy	13	9	0
Israel	1	0	0
Australia	2	1	0
France	34	17	0
Germany	12	3	8

Reporting group values	Ramucirumab MEE Cohort	Placebo MEE Cohort	Total
Number of subjects	70	34	443
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0

85 years and over			0

Age continuous Units: years			
median	57	55	
full range (min-max)	24 to 80	31 to 76	-
Gender categorical Units: Subjects			
Female	15	3	83
Male	55	31	360
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	0	22
Not Hispanic or Latino	40	21	288
Unknown or Not Reported	30	13	133
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	70	34	277
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	6
White	0	0	104
More than one race	0	0	5
Unknown or Not Reported	0	0	51
Region of Enrollment Units: Subjects			
Hong Kong	6	1	22
United States	0	0	23
Czechia	0	0	6
Japan	0	0	59
United Kingdom	0	0	11
Switzerland	0	0	5
Spain	0	0	5
Canada	0	0	2
Austria	0	0	2
South Korea	0	0	38
Belgium	0	0	4
China	42	22	76
Taiwan	22	11	76
Brazil	0	0	9
Poland	0	0	5
Italy	0	0	22
Israel	0	0	1
Australia	0	0	3
France	0	0	51
Germany	0	0	23

Subject analysis sets

Subject analysis set title	Placebo + Best Supportive Care (BSC)
Subject analysis set type	Per protocol

Subject analysis set description:

Placebo administered IV on day 1 of each 14 day cycle. Participants may continue treatment until discontinuation criteria are met.
Participants still on treatment at the time of study completion may have the option to crossover to the ramucirumab arm.

Subject analysis set title	Ramucirumab + Best Supportive Care (BSC)
Subject analysis set type	Per protocol

Subject analysis set description:

8 milligrams per kilogram (mg/kg) ramucirumab administered as an intravenous (IV) injection on day 1 of each 14 day cycle. Participants may continue treatment until discontinuation criteria are met.

Subject analysis set title	Ramucirumab + BSC
Subject analysis set type	Per protocol

Subject analysis set description:

8 mg/kg ramucirumab administered as an intravenous IV injection on day 1 of each 14 day cycle. Participants may continue treatment until discontinuation criteria are met.

Reporting group values	Placebo + Best Supportive Care (BSC)	Ramucirumab + Best Supportive Care (BSC)	Ramucirumab + BSC
Number of subjects	95	197	197
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
median			
full range (min-max)			
Gender categorical Units: Subjects			
Female			
Male			
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	9		
Not Hispanic or Latino	58		
Unknown or Not Reported	28		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	45		

Native Hawaiian or Other Pacific Islander	0		
Black or African American	1		
White	31		
More than one race	1		
Unknown or Not Reported	17		
Region of Enrollment Units: Subjects			
Hong Kong	1		
United States	1		
Czechia	2		
Japan	18		
United Kingdom	2		
Switzerland	2		
Spain	2		
Canada	1		
Austria	1		
South Korea	14		
Belgium	2		
China	1		
Taiwan	11		
Brazil	4		
Poland	3		
Italy	9		
Israel	0		
Australia	1		
France	17		
Germany	3		

End points

End points reporting groups

Reporting group title	Ramucirumab + BSC

Reporting group description:

8 milligrams per kilogram (mg/kg) ramucirumab administered as an intravenous (IV) injection on day 1 of each 14-day cycle. Participants may continue treatment until discontinuation criteria are met.

Reporting group title	Placebo + BSC

Reporting group description:

Placebo administered IV on day 1 of each 14 day cycle. Participants may continue treatment until discontinuation criteria are met.

Reporting group title	Open Label Ramucirumab + BSC

Reporting group description:

8 mg/kg ramucirumab administered IV on day 1 of each 14 day cycle. Participants may continue treatment until discontinuation criteria are met.

Reporting group title	Ramucirumab MEE Cohort

Reporting group description:

8 mg/kg ramucirumab administered IV on day 1 of each 14-day cycle. Participants may continue treatment until discontinuation criteria are met.

Number of participants: 31 (main study) + 39 (new enrolment)

Reporting group title	Placebo MEE Cohort

Reporting group description:

Placebo administered IV on day 1 of each 14-day cycle. Participants may continue treatment until discontinuation criteria are met.

Number of participants: 13 (main study) + 21 (new enrolment)

Subject analysis set title	Placebo + Best Supportive Care (BSC)
Subject analysis set type	Per protocol

Subject analysis set description:

Placebo administered IV on day 1 of each 14 day cycle. Participants may continue treatment until discontinuation criteria are met.
Participants still on treatment at the time of study completion may have the option to crossover to the ramucirumab arm.

Subject analysis set title	Ramucirumab + Best Supportive Care (BSC)
Subject analysis set type	Per protocol

Subject analysis set description:

8 milligrams per kilogram (mg/kg) ramucirumab administered as an intravenous (IV) injection on day 1 of each 14 day cycle. Participants may continue treatment until discontinuation criteria are met.

Subject analysis set title	Ramucirumab + BSC
Subject analysis set type	Per protocol

Subject analysis set description:

8 mg/kg ramucirumab administered as an intravenous IV injection on day 1 of each 14 day cycle. Participants may continue treatment until discontinuation criteria are met.

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)[1]

End point description:

OS time was measured from date of randomization to date of death from any cause. Participants who were not known to have died on or before the date of data cut-off, OS data was censored on the last date (on or before the cut-off date) the participant was known to be alive.

Analysis Population Description (APD): All randomized participants. Participants were censored in Ramucirumab arm = 50 and Placebo arm = 21. All randomized participants (including the censored participants) were included in the analyses.

End point type	Primary

End point timeframe:

From Date of Randomization to Death from Any Cause (Up to 28 Months)

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistical analyses were performed only for the main study arms as per the study statistical analysis plan.

End point values	Placebo + BSC	Ramucirumab + Best Supportive Care (BSC)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	95	197		
Units: Months				
median (confidence interval 95%)	7.29 (5.42 to 9.07)	8.51 (7.00 to 10.58)		

Statistical analyses

Statistical analysis title	Overall Survival (OS)
Comparison groups	Placebo + BSC v Ramucirumab + Best Supportive Care (BSC)
Number of subjects included in analysis	292
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0199
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.531
upper limit	0.949

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)[2]

End point description:

Progression-free survival is defined as time from the date of randomization to the date of first observation of objective progression or death from any cause.
APD: All randomized participants. Participants were censored in the Ramucirumab arm = 25 and in the Placebo arm = 9. All randomized participants (including the censored participants) were included in the analyses.

End point type	Secondary

End point timeframe:

From Randomization to Objective Progression or Death from Any Cause (Up to 28 Months)

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistical analyses were performed only for the main study arms as per the study statistical analysis plan.

End point values	Ramucirumab + BSC	Placebo + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	197	95		
Units: Months				
median (confidence interval 95%)	2.83 (2.76 to 4.11)	1.61 (1.45 to 2.69)		

Statistical analyses

Statistical analysis title	Progression Free Survival (PFS)
Comparison groups	Ramucirumab + BSC v Placebo + BSC
Number of subjects included in analysis	292
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.452
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.339
upper limit	0.603

Secondary: Time to Radiographic Progression

End point title	Time to Radiographic Progression[3]

End point description:

Time to radiographic progression is defined as the time from the date of randomization to the date of first observation of objective progression.
APD: All randomized participants.

End point type	Secondary

End point timeframe:

From Randomization to Objective Progression (Up to 28 Months)

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistical analyses were performed only for the main study arms as per the study statistical analysis plan.

End point values	Ramucirumab + BSC	Placebo + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	197	95		
Units: Months				
median (confidence interval 95%)	3.02 (2.79 to 4.17)	1.61 (1.45 to 2.73)		

Statistical analyses

Statistical analysis title	Time to Radiographic Progression
Comparison groups	Ramucirumab + BSC v Placebo + BSC
Number of subjects included in analysis	292
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.427
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.313
upper limit	0.582

Secondary: Percentage of Participants with a Best Overall Response of Complete Response (CR) or Partial Response (PR): Objective Response Rate (ORR)

End point title	Percentage of Participants with a Best Overall Response of Complete Response (CR) or Partial Response (PR): Objective Response Rate (ORR)[4]

End point description:

Objective response rate is defined as the percentage of participants who achieve a best overall response of complete response (CR) + partial response (PR). ORR = CR + PR. CR is the disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (<10 mm short axis). PR is at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. CR: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. Tumor marker results must have normalized. Best overall response is classified based on the overall responses assessed by study investigators according to Response Evaluation Criteria In Solid Tumors (RECIST) Version 1.1.
APD: All randomized participants who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

From Randomization to Objective Progression (Up to 28 Months)

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistical analyses were performed only for the main study arms as per the study statistical analysis plan.

End point values	Ramucirumab + BSC	Placebo + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	197	95		
Units: percentage of participants				
number (not applicable)	4.6	1.1		

Statistical analyses

Statistical analysis title	Percentage of Participants with a Best Overall Re
Comparison groups	Ramucirumab + BSC v Placebo + BSC
Number of subjects included in analysis	292
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1697
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	4.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	37.3

Secondary: Pharmacokinetics (PK): Minimum Serum Concentration (Cmin) Before 2nd, 4th, 7th, and 10th Infusion

End point title	Pharmacokinetics (PK): Minimum Serum Concentration (Cmin) Before 2nd, 4th, 7th, and 10th Infusion[5]

End point description:

PK Cmin of Ramucirumab Blood samples were collected at specified time points, and in the event of an infusion-related reaction, for assessment of ramucirumab serum concentrations.
APD: All randomized participants who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Predose, Weeks 2, 6, 12 and 18, Day 1; Up to 3 Days Before Infusion (14-Day Cycles)

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistical analyses were performed only for the main study arms as per the study statistical analysis plan.PK analyses were done only in main study participants who received Ramucirumab.

End point values	Ramucirumab + BSC			
Subject group type	Reporting group			
Number of subjects analysed	195			
Units: nanogram/milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)				
Week 0	0 (± 0)			

Week 2	23.5 (± 57)			
Week 6	44.1 (± 60)			
Week 12	60.2 (± 46)			
Week 18	63.2 (± 40)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK: Serum Concentration Maximum (Cmax) After 1st, 2nd, 4th, 7th and 10th Ram Infusion

End point title	PK: Serum Concentration Maximum (Cmax) After 1st, 2nd, 4th, 7th and 10th Ram Infusion[6]

End point description:

PK Cmax of Ramucirumab Blood samples were collected at specified time points, and in the event of an infusion-related reaction, for assessment of ramucirumab serum concentrations.
APD: All randomized participants who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Weeks 0, 2, 6, 12 and 18, Day 1; 1 hour to 1.5 hours Post End of Infusion (14 day-Cycles)

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistical analyses were performed only for the main study arms as per the study statistical analysis plan.PK analyses were done only in main study participants who received Ramucirumab.

End point values	Ramucirumab + BSC			
Subject group type	Reporting group			
Number of subjects analysed	195			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Week 0	156 (± 22)			
Week 2	181 (± 24)			
Week 6	205 (± 24)			
Week 12	221 (± 24)			
Week 18	228 (± 22)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Anti-Ramucirumab Antibodies

End point title	Percentage of Participants with Anti-Ramucirumab Antibodies[7]

End point description:

Percentage of participants with positive treatment emergent anti-drug antibodies was summarized by treatment group. A treatment-emergent ADA (TEADA) was defined as: having a negative ADA at baseline and an ADA titer greater than or equal to 1:20 (that is (i.e.), greater than 2-fold from the

minimal required dilution of 1:10) any time post baseline (i.e., treatment-induced); or a 4-fold or greater change in ADA titer from baseline for participants that had a detectable ADA titer at baseline (i.e., treatment boosted).
APD: All randomized participants who received at least one dose of study drug and had evaluable anti-ramucirumab data.

End point type	Secondary

End point timeframe:

Predose Cycle 1: 7 Days prior to First Infusion, Cycle 4: 3 Days Prior to Infusion, Cycle 7 through Follow Up (Up to 28 Months)

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistical analyses were performed only for the main study arms as per the study statistical analysis plan.

End point values	Ramucirumab + BSC	Placebo + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	161	76		
Units: percentage of participants				
number (not applicable)	5.0	9.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Deterioration of Functional Assessment of Cancer Therapy (FACT) Hepatobiliary Symptom Index-8 (FHSI-8)

End point title	Time to Deterioration of Functional Assessment of Cancer Therapy (FACT) Hepatobiliary Symptom Index-8 (FHSI-8)[8]

End point description:

The FACT Hepatobiliary Symptom Index (FHSI-8) is a instrument with specific focus regarding the most frequent and concerning symptoms experienced by participants with hepatobiliary malignancies, including lack of energy, nausea, pain, weight loss, pain in back, fatigue, jaundice, stomach pain or discomfort. The (FHSI-8) questionnaire was used to assess the time to deterioration of FSHI-8 total score with the deterioration threshold defined as a decrease ≥ 3-points from baseline. In case of no deterioration, the participants were censored at the time of the last FSHI-8 item recording. FHSI-8 total score ranges from 0 to 32 where "0" is a severely symptomatic participant and the highest score indicates an asymptomatic participant. Kaplan-Meier method Hazard ratio was used to estimate (Ramucirumab versus Placebo) and 95% Confidence Interval (CI) (Wald) were estimated from un-stratified/stratified Cox model.
APD: All randomized participants who had evaluable FHSI-8 data.

End point type	Secondary

End point timeframe:

From Randomization to the First Date of Deterioration Observation (≥ 3-point decrease) (Up to 28 Months)

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistical analyses were performed only for the main study arms as per the study statistical analysis plan.

End point values	Ramucirumab + BSC	Placebo + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	197	95		
Units: Months				
median (confidence interval 95%)	3.71 (2.79 to 4.40)	2.79 (1.64 to 2.89)		

Statistical analyses

Statistical analysis title	Time to Deterioration of Functional Assessment of
Comparison groups	Ramucirumab + BSC v Placebo + BSC
Number of subjects included in analysis	292
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2382
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.799
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.545
upper limit	1.171

Secondary: Change from Baseline in EuroQol 5-Dimension 5-Level (EQ-5D-5L) Questionnaire

End point title	Change from Baseline in EuroQol 5-Dimension 5-Level (EQ-5D-5L) Questionnaire[9]

End point description:

The EQ-5D-5L is a nonspecific and standardized instrument for use as a measure of self-reported health status (EuroQol Group 1990; Herdman et al. 2011). Participants completed the 5-level (no problems, slight problems, moderate problems, severe problems, and extreme problems), 5-dimension (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) questionnaire concerning their current health state. A unique EQ-5D-5L health state scale ranges from 0 to 100 and is defined by combining 1 level from each of the 5 dimensions. Participants indicated their current health status by marking on a continuum ranging from 100 (best imaginable health state) to 0 (worst imaginable health state).
APD: All randomized participants and had evaluable EQ-5D-5L data.

End point type	Secondary

End point timeframe:

From Randomization through End of Study (Up to 28 Months)

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistical analyses were performed only for the main study arms as per the study statistical analysis plan.

End point values	Ramucirumab + BSC	Placebo + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	197	95		
Units: units on a scale				
arithmetic mean (standard deviation)	-0.105 (± 0.201)	-0.099 (± 0.170)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Deterioration in Eastern Cooperative Oncology Group Performance Status (ECOG PS)

End point title	Time to Deterioration in Eastern Cooperative Oncology Group Performance Status (ECOG PS)[10]

End point description:

Time to deterioration in ECOG PS is defined as the time from the date of randomization to the first date observing ECOG PS 2 (ie, deterioration from baseline status of 0 [fully active] or 1 [restricted in physically strenuous activity but ambulatory and able to carry out light work]). Participants without PS deterioration were censored at their last documented assessments of 0 or 1. Assessments included ECOG Performance Status (PS): 2- Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours, 3 -Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours, 4 -Completely disabled, cannot carry on any self-care. Totally confined to bed or chair, 5- Dead.
APD: All randomized participants and had evaluable ECOG data. Censored participants without any post baseline assessments at randomization date were in the Ramucirumab + BSC arm = 141 and the Placebo + BSC arm =75.

End point type	Secondary

End point timeframe:

From Randomization through First Date of Deterioration Observation (ECOG PS≥2) (Up to 28 Months)

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistical analyses were performed only for the main study arms as per the study statistical analysis plan.

End point values	Ramucirumab + BSC	Placebo + BSC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	197[11]	95[12]		
Units: Months				
median (confidence interval 95%)	9999 (9.33 to 9999)	9999 (5.26 to 9999)		

Notes:

[11] - The median and 95% CI upper limit had insufficient events to perform a stat evaluation; 9999=N/A.
[12] - The median and 95% CI upper limit had insufficient events to perform a stat evaluation; 9999=N/A.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 3.2 years

Adverse event reporting additional description:

All participants who received at least one dose of study drug. Gender specific events only occurring in male or female participants have had the number of participants at risk adjusted accordingly.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Ramucirumab + BSC

Reporting group description:

8 milligrams per kilogram (mg/kg) ramucirumab administered as an intravenous (IV) injection on day 1 of each 14 day cycle. Participants may continue treatment until discontinuation criteria are met.

Reporting group title	Placebo+BSC

Reporting group description:

Placebo administered IV on day 1 of each 14 day cycle. Participants may continue treatment until discontinuation criteria are met. Participants still on treatment at the time of study completion may have the option to crossover to the ramucirumab arm

Reporting group title	Ramucirumab MEE Cohort

Reporting group description:

8 mg/kg ramucirumab administered IV on day 1 of each 14 day cycle. Participants may continue treatment until discontinuation criteria are met.
Number of participants: 31 (main study) + 39 (new enrolment)

Reporting group title	Placebo MEE Cohort

Reporting group description:

Placebo administered IV on day 1 of each 14 day cycle. Participants may continue treatment until discontinuation criteria are met. Participants still on treatment at the time of study completion may have the option to crossover to the ramucirumab arm.
Number of participants: 13 (main study) + 21 (new enrolment)

Reporting group title	Open Label Ramucirumab + BSC

Reporting group description:

8 mg/kg ramucirumab administered IV on day 1 of each 14 day cycle. Participants may continue treatment until discontinuation criteria are met.

Serious adverse events	Ramucirumab + BSC	Placebo+BSC	Ramucirumab MEE Cohort
Total subjects affected by serious adverse events			
subjects affected / exposed	72 / 197 (36.55%)	27 / 95 (28.42%)	19 / 70 (27.14%)
number of deaths (all causes)	162	76	35
number of deaths resulting from adverse events	10	3	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
liver carcinoma ruptured			
alternative dictionary used: MedDRA 25.0			

subjects affected / exposed	0 / 197 (0.00%)	1 / 95 (1.05%)	0 / 70 (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
metastases to bone			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 197 (0.51%)	0 / 95 (0.00%)	0 / 70 (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
metastases to spine			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 197 (0.51%)	1 / 95 (1.05%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
tumour haemorrhage			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 197 (0.51%)	0 / 95 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
tumour pain			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 197 (0.51%)	0 / 95 (0.00%)	0 / 70 (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
tumour rupture			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 197 (0.51%)	0 / 95 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Vascular disorders			
deep vein thrombosis			
alternative dictionary used: MedDRA 25.0			

subjects affected / exposed	0 / 197 (0.00%)	1 / 95 (1.05%)	0 / 70 (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
haemorrhage			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 197 (0.00%)	1 / 95 (1.05%)	0 / 70 (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
hypertensive crisis			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 197 (0.51%)	0 / 95 (0.00%)	0 / 70 (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
thrombophlebitis migrans			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 197 (0.51%)	0 / 95 (0.00%)	0 / 70 (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
Surgical and medical procedures			
tumour excision			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 197 (0.00%)	0 / 95 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
asthenia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 197 (0.51%)	0 / 95 (0.00%)	0 / 70 (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
general physical health deterioration			
alternative dictionary used: MedDRA 25.0			

subjects affected / exposed	2 / 197 (1.02%)	0 / 95 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
generalised oedema			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 197 (0.51%)	0 / 95 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
multiple organ dysfunction syndrome			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 197 (0.51%)	0 / 95 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
oedema peripheral			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	3 / 197 (1.52%)	0 / 95 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pain			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 197 (0.00%)	0 / 95 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pyrexia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	3 / 197 (1.52%)	1 / 95 (1.05%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
anaphylactic reaction			
alternative dictionary used: MedDRA 25.0			

subjects affected / exposed	1 / 197 (0.51%)	0 / 95 (0.00%)	0 / 70 (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
Respiratory, thoracic and mediastinal disorders			
dyspnoea			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	3 / 197 (1.52%)	2 / 95 (2.11%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
epistaxis			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 197 (0.51%)	0 / 95 (0.00%)	0 / 70 (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
haemothorax			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 197 (0.51%)	0 / 95 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hypoxia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 197 (0.00%)	0 / 95 (0.00%)	0 / 70 (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
lung disorder			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 197 (0.00%)	1 / 95 (1.05%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
pleural effusion			
alternative dictionary used: MedDRA 25.0			

subjects affected / exposed	0 / 197 (0.00%)	1 / 95 (1.05%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pulmonary oedema			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 197 (0.00%)	1 / 95 (1.05%)	0 / 70 (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
respiratory failure			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 197 (0.00%)	0 / 95 (0.00%)	0 / 70 (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
Psychiatric disorders			
anxiety			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 197 (0.00%)	1 / 95 (1.05%)	0 / 70 (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
confusional state			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 197 (0.51%)	0 / 95 (0.00%)	0 / 70 (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
mental status changes			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 197 (0.00%)	0 / 95 (0.00%)	0 / 70 (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
Investigations			
aspartate aminotransferase increased			
alternative dictionary used: MedDRA 25.0			

subjects affected / exposed	0 / 197 (0.00%)	0 / 95 (0.00%)	0 / 70 (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
aspiration pleural cavity			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 197 (0.51%)	0 / 95 (0.00%)	0 / 70 (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
blood bilirubin increased			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 197 (0.00%)	1 / 95 (1.05%)	0 / 70 (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
general physical condition abnormal			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 197 (0.51%)	0 / 95 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Injury, poisoning and procedural complications			
ankle fracture			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 197 (0.00%)	1 / 95 (1.05%)	0 / 70 (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
fall			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 197 (0.51%)	0 / 95 (0.00%)	0 / 70 (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
hip fracture			
alternative dictionary used: MedDRA 25.0			

subjects affected / exposed	1 / 197 (0.51%)	0 / 95 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
infusion related reaction			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 197 (0.00%)	1 / 95 (1.05%)	0 / 70 (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
Cardiac disorders			
acute coronary syndrome			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 197 (0.00%)	0 / 95 (0.00%)	0 / 70 (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
angina pectoris			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 197 (0.51%)	0 / 95 (0.00%)	0 / 70 (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
cardiac arrest			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 197 (0.51%)	0 / 95 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
myocardial infarction			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 197 (0.51%)	1 / 95 (1.05%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Nervous system disorders			
cerebral ischaemia			
alternative dictionary used: MedDRA 25.0			

subjects affected / exposed	1 / 197 (0.51%)	0 / 95 (0.00%)	0 / 70 (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
cerebrovascular accident			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 197 (0.51%)	0 / 95 (0.00%)	0 / 70 (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
coma hepatic			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 197 (0.51%)	0 / 95 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
epilepsy			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 197 (0.51%)	0 / 95 (0.00%)	0 / 70 (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
hepatic encephalopathy			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	3 / 197 (1.52%)	0 / 95 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
somnolence			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 197 (0.51%)	0 / 95 (0.00%)	0 / 70 (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
syncope			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 197 (0.00%)	0 / 95 (0.00%)	0 / 70 (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

Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 197 (0.00%)	0 / 95 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
neutropenia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 197 (0.51%)	0 / 95 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
splenic infarction			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 197 (0.51%)	0 / 95 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Gastrointestinal disorders			
abdominal hernia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 197 (0.51%)	0 / 95 (0.00%)	0 / 70 (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
abdominal pain			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	3 / 197 (1.52%)	0 / 95 (0.00%)	2 / 70 (2.86%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
abdominal pain upper			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 197 (0.51%)	0 / 95 (0.00%)	0 / 70 (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
ascites			
alternative dictionary used: MedDRA 25.0			

subjects affected / exposed	6 / 197 (3.05%)	0 / 95 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	1 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
colitis			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 197 (0.51%)	0 / 95 (0.00%)	0 / 70 (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
constipation			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 197 (0.00%)	1 / 95 (1.05%)	0 / 70 (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
enterocolitis			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 197 (0.00%)	1 / 95 (1.05%)	0 / 70 (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
gastric haemorrhage			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 197 (0.51%)	0 / 95 (0.00%)	0 / 70 (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
gastric perforation			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 197 (0.51%)	0 / 95 (0.00%)	0 / 70 (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
gastric ulcer			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 197 (0.51%)	0 / 95 (0.00%)	0 / 70 (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

gastric varices haemorrhage alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 197 (0.00%)	0 / 95 (0.00%)	0 / 70 (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
gastroduodenal ulcer alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 197 (0.51%)	0 / 95 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
gastrointestinal haemorrhage alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 197 (0.00%)	1 / 95 (1.05%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 0	0 / 1	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
lower gastrointestinal haemorrhage alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 197 (0.51%)	0 / 95 (0.00%)	0 / 70 (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
melaena alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 197 (0.00%)	1 / 95 (1.05%)	0 / 70 (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
mouth ulceration alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 197 (0.00%)	0 / 95 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
nausea alternative dictionary used: MedDRA 25.0			

subjects affected / exposed	0 / 197 (0.00%)	1 / 95 (1.05%)	0 / 70 (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
oesophageal haemorrhage			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 197 (0.51%)	0 / 95 (0.00%)	0 / 70 (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 varices haemorrhage			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	2 / 197 (1.02%)	1 / 95 (1.05%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 2	0 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
rectal haemorrhage			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 197 (0.51%)	0 / 95 (0.00%)	0 / 70 (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 25.0			
subjects affected / exposed	1 / 197 (0.51%)	0 / 95 (0.00%)	3 / 70 (4.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
varices oesophageal			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 197 (0.51%)	0 / 95 (0.00%)	0 / 70 (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
Hepatobiliary disorders			
acute hepatic failure			
alternative dictionary used: MedDRA 25.0			

subjects affected / exposed	1 / 197 (0.51%)	0 / 95 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
cholestasis			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 197 (0.00%)	1 / 95 (1.05%)	0 / 70 (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
hepatic cirrhosis			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 197 (0.00%)	0 / 95 (0.00%)	1 / 70 (1.43%)
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 function abnormal			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 197 (0.00%)	0 / 95 (0.00%)	0 / 70 (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
hepatic pain			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 197 (0.00%)	0 / 95 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hepatorenal syndrome			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	2 / 197 (1.02%)	0 / 95 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
jaundice			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 197 (0.51%)	1 / 95 (1.05%)	0 / 70 (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

Renal and urinary disorders			
acute kidney injury			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	3 / 197 (1.52%)	0 / 95 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
haematuria			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 197 (0.00%)	0 / 95 (0.00%)	0 / 70 (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
nephrotic syndrome			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 197 (0.51%)	0 / 95 (0.00%)	0 / 70 (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
renal failure			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 197 (0.51%)	0 / 95 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
back pain			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 197 (0.51%)	0 / 95 (0.00%)	0 / 70 (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
muscular weakness			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 197 (0.51%)	0 / 95 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			

abdominal infection			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 197 (0.00%)	0 / 95 (0.00%)	0 / 70 (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
anal abscess			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 197 (0.51%)	0 / 95 (0.00%)	0 / 70 (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
appendicitis			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 197 (0.51%)	1 / 95 (1.05%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
gastroenteritis			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 197 (0.51%)	0 / 95 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
infection			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 197 (0.00%)	1 / 95 (1.05%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
influenza			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	2 / 197 (1.02%)	0 / 95 (0.00%)	0 / 70 (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
lower respiratory tract infection			
alternative dictionary used: MedDRA 25.0			

subjects affected / exposed	2 / 197 (1.02%)	0 / 95 (0.00%)	0 / 70 (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
peritonitis			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 197 (0.51%)	2 / 95 (2.11%)	0 / 70 (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
pleural infection			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 197 (0.51%)	0 / 95 (0.00%)	0 / 70 (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
pneumonia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	5 / 197 (2.54%)	3 / 95 (3.16%)	5 / 70 (7.14%)
occurrences causally related to treatment / all	1 / 5	0 / 4	0 / 5
deaths causally related to treatment / all	0 / 2	0 / 1	0 / 2
post procedural infection			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 197 (0.51%)	0 / 95 (0.00%)	0 / 70 (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
post procedural pneumonia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 197 (0.00%)	0 / 95 (0.00%)	0 / 70 (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
respiratory tract infection			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 197 (0.00%)	1 / 95 (1.05%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

sepsis			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	3 / 197 (1.52%)	3 / 95 (3.16%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
septic shock			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 197 (0.00%)	1 / 95 (1.05%)	0 / 70 (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
urinary tract infection			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 197 (0.51%)	0 / 95 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
decreased appetite			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 197 (0.51%)	0 / 95 (0.00%)	0 / 70 (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
dehydration			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 197 (0.51%)	0 / 95 (0.00%)	0 / 70 (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
hypercalcaemia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 197 (0.00%)	1 / 95 (1.05%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hyponatraemia			
alternative dictionary used: MedDRA 25.0			

subjects affected / exposed	0 / 197 (0.00%)	0 / 95 (0.00%)	0 / 70 (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	Placebo MEE Cohort	Open Label Ramucirumab + BSC	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 34 (26.47%)	18 / 47 (38.30%)	
number of deaths (all causes)	18	33	
number of deaths resulting from adverse events	0	5	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
liver carcinoma ruptured			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
metastases to bone			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
metastases to spine			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 34 (2.94%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
tumour haemorrhage			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
tumour pain			
alternative dictionary used: MedDRA 25.0			

subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
tumour rupture			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
deep vein thrombosis			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
haemorrhage			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypertensive crisis			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
thrombophlebitis migrans			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
tumour excision			
alternative dictionary used: MedDRA 25.0			

subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
asthenia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
general physical health deterioration			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
generalised oedema			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
multiple organ dysfunction syndrome			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
oedema peripheral			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pain			
alternative dictionary used: MedDRA 25.0			

subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pyrexia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	2 / 47 (4.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
anaphylactic reaction			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
dyspnoea			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
epistaxis			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
haemothorax			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypoxia			
alternative dictionary used: MedDRA 25.0			

subjects affected / exposed	0 / 34 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
lung disorder			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pleural effusion			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pulmonary oedema			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 34 (2.94%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
respiratory failure			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
anxiety			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
confusional state			
alternative dictionary used: MedDRA 25.0			

subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
mental status changes			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
aspartate aminotransferase increased			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
aspiration pleural cavity			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
blood bilirubin increased			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
general physical condition abnormal			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
ankle fracture			
alternative dictionary used: MedDRA 25.0			

subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
fall			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hip fracture			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
infusion related reaction			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
acute coronary syndrome			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
angina pectoris			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
cardiac arrest			
alternative dictionary used: MedDRA 25.0			

subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
myocardial infarction			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Nervous system disorders			
cerebral ischaemia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
cerebrovascular accident			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
coma hepatic			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
epilepsy			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hepatic encephalopathy			
alternative dictionary used: MedDRA 25.0			

subjects affected / exposed	1 / 34 (2.94%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
somnolence			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
syncope			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 47 (2.13%)	
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 25.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
neutropenia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
splenic infarction			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
abdominal hernia			
alternative dictionary used: MedDRA 25.0			

subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
abdominal pain			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
abdominal pain upper			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ascites			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
colitis			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
constipation			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
enterocolitis			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

gastric haemorrhage				
alternative dictionary used: MedDRA 25.0				
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
gastric perforation				
alternative dictionary used: MedDRA 25.0				
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
gastric ulcer				
alternative dictionary used: MedDRA 25.0				
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
gastric varices haemorrhage				
alternative dictionary used: MedDRA 25.0				
subjects affected / exposed	0 / 34 (0.00%)	1 / 47 (2.13%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
gastroduodenal ulcer				
alternative dictionary used: MedDRA 25.0				
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)		
occurrences causally related to treatment / all	0 / 0	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
gastrointestinal haemorrhage				
alternative dictionary used: MedDRA 25.0				
subjects affected / exposed	0 / 34 (0.00%)	1 / 47 (2.13%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
lower gastrointestinal haemorrhage				
alternative dictionary used: MedDRA 25.0				

subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
melaena			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 34 (2.94%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
mouth ulceration			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
nausea			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
oesophageal haemorrhage			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
oesophageal varices haemorrhage			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
rectal haemorrhage			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

upper gastrointestinal haemorrhage			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
varices oesophageal			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
acute hepatic failure			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
cholestasis			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hepatic cirrhosis			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
hepatic function abnormal			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 34 (2.94%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hepatic pain			
alternative dictionary used: MedDRA 25.0			

subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hepatorenal syndrome			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
jaundice			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
acute kidney injury			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
haematuria			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
nephrotic syndrome			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
renal failure			
alternative dictionary used: MedDRA 25.0			

subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
back pain			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
muscular weakness			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
abdominal infection			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 34 (2.94%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
anal abscess			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
appendicitis			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 34 (2.94%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
gastroenteritis			
alternative dictionary used: MedDRA 25.0			

subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
infection			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
influenza			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
lower respiratory tract infection			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
peritonitis			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 34 (2.94%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pleural infection			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pneumonia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	2 / 47 (4.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	

post procedural infection			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
post procedural pneumonia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
respiratory tract infection			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
sepsis			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 34 (2.94%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
septic shock			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 34 (2.94%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
urinary tract infection			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
decreased appetite			
alternative dictionary used: MedDRA 25.0			

subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
dehydration			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypercalcaemia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 34 (2.94%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hyponatraemia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Ramucirumab + BSC	Placebo+BSC	Ramucirumab MEE Cohort
Total subjects affected by non-serious adverse events			
subjects affected / exposed	189 / 197 (95.94%)	77 / 95 (81.05%)	68 / 70 (97.14%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
tumour pain			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	4 / 197 (2.03%)	8 / 95 (8.42%)	0 / 70 (0.00%)
occurrences (all)	4	9	0
Vascular disorders			
hypertension			
alternative dictionary used: MedDRA 25.0			

subjects affected / exposed	50 / 197 (25.38%)	12 / 95 (12.63%)	13 / 70 (18.57%)
occurrences (all)	79	13	18
General disorders and administration site conditions			
asthenia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	17 / 197 (8.63%)	3 / 95 (3.16%)	0 / 70 (0.00%)
occurrences (all)	41	6	0
chills			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 197 (0.00%)	5 / 95 (5.26%)	1 / 70 (1.43%)
occurrences (all)	0	6	1
fatigue			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	54 / 197 (27.41%)	16 / 95 (16.84%)	8 / 70 (11.43%)
occurrences (all)	79	23	9
influenza like illness			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	10 / 197 (5.08%)	1 / 95 (1.05%)	1 / 70 (1.43%)
occurrences (all)	10	1	1
malaise			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	16 / 197 (8.12%)	5 / 95 (5.26%)	6 / 70 (8.57%)
occurrences (all)	19	6	13
oedema			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	6 / 197 (3.05%)	1 / 95 (1.05%)	1 / 70 (1.43%)
occurrences (all)	6	1	1
oedema peripheral			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	52 / 197 (26.40%)	13 / 95 (13.68%)	15 / 70 (21.43%)
occurrences (all)	69	13	23
pyrexia			
alternative dictionary used: MedDRA 25.0			

subjects affected / exposed	19 / 197 (9.64%)	3 / 95 (3.16%)	7 / 70 (10.00%)
occurrences (all)	23	3	9
Reproductive system and breast disorders			
dysmenorrhoea			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed[1]	1 / 43 (2.33%)	0 / 16 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
endometrial hyperplasia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed[2]	1 / 43 (2.33%)	0 / 16 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Respiratory, thoracic and mediastinal disorders			
cough			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	21 / 197 (10.66%)	6 / 95 (6.32%)	9 / 70 (12.86%)
occurrences (all)	26	7	9
dysphonia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	12 / 197 (6.09%)	1 / 95 (1.05%)	1 / 70 (1.43%)
occurrences (all)	12	1	1
dyspnoea			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	16 / 197 (8.12%)	8 / 95 (8.42%)	0 / 70 (0.00%)
occurrences (all)	19	9	0
epistaxis			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	27 / 197 (13.71%)	3 / 95 (3.16%)	1 / 70 (1.43%)
occurrences (all)	31	3	2
Psychiatric disorders			
insomnia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	21 / 197 (10.66%)	6 / 95 (6.32%)	5 / 70 (7.14%)
occurrences (all)	24	8	5
Investigations			

alanine aminotransferase increased			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	7 / 197 (3.55%)	5 / 95 (5.26%)	12 / 70 (17.14%)
occurrences (all)	12	6	19
aspartate aminotransferase increased			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	16 / 197 (8.12%)	10 / 95 (10.53%)	18 / 70 (25.71%)
occurrences (all)	27	15	30
bilirubin conjugated increased			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 197 (0.00%)	0 / 95 (0.00%)	2 / 70 (2.86%)
occurrences (all)	0	0	2
blood albumin decreased			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 197 (0.00%)	0 / 95 (0.00%)	4 / 70 (5.71%)
occurrences (all)	0	0	6
blood alkaline phosphatase increased			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	4 / 197 (2.03%)	2 / 95 (2.11%)	1 / 70 (1.43%)
occurrences (all)	4	2	1
blood bilirubin increased			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	21 / 197 (10.66%)	8 / 95 (8.42%)	14 / 70 (20.00%)
occurrences (all)	39	16	33
gamma-glutamyltransferase increased			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	2 / 197 (1.02%)	5 / 95 (5.26%)	3 / 70 (4.29%)
occurrences (all)	2	6	3
neutrophil count decreased			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	12 / 197 (6.09%)	0 / 95 (0.00%)	10 / 70 (14.29%)
occurrences (all)	30	0	18
platelet count decreased			
alternative dictionary used: MedDRA 25.0			

subjects affected / exposed	23 / 197 (11.68%)	2 / 95 (2.11%)	22 / 70 (31.43%)
occurrences (all)	72	3	53
weight decreased			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	22 / 197 (11.17%)	6 / 95 (6.32%)	5 / 70 (7.14%)
occurrences (all)	25	7	5
white blood cell count decreased			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	7 / 197 (3.55%)	0 / 95 (0.00%)	8 / 70 (11.43%)
occurrences (all)	26	0	24
Nervous system disorders			
dizziness			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	9 / 197 (4.57%)	8 / 95 (8.42%)	3 / 70 (4.29%)
occurrences (all)	10	8	3
headache			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	28 / 197 (14.21%)	5 / 95 (5.26%)	5 / 70 (7.14%)
occurrences (all)	36	5	8
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	19 / 197 (9.64%)	6 / 95 (6.32%)	12 / 70 (17.14%)
occurrences (all)	28	7	21
thrombocytopenia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	7 / 197 (3.55%)	1 / 95 (1.05%)	2 / 70 (2.86%)
occurrences (all)	16	1	2
Gastrointestinal disorders			
abdominal distension			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	16 / 197 (8.12%)	5 / 95 (5.26%)	8 / 70 (11.43%)
occurrences (all)	18	6	8
abdominal pain			
alternative dictionary used: MedDRA 25.0			

subjects affected / exposed	36 / 197 (18.27%)	12 / 95 (12.63%)	10 / 70 (14.29%)
occurrences (all)	46	16	13
abdominal pain upper			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	10 / 197 (5.08%)	3 / 95 (3.16%)	4 / 70 (5.71%)
occurrences (all)	10	3	4
ascites			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	34 / 197 (17.26%)	7 / 95 (7.37%)	8 / 70 (11.43%)
occurrences (all)	47	7	9
constipation			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	27 / 197 (13.71%)	18 / 95 (18.95%)	4 / 70 (5.71%)
occurrences (all)	33	19	4
diarrhoea			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	33 / 197 (16.75%)	14 / 95 (14.74%)	3 / 70 (4.29%)
occurrences (all)	46	18	5
mouth ulceration			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 197 (0.00%)	0 / 95 (0.00%)	4 / 70 (5.71%)
occurrences (all)	0	0	4
nausea			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	37 / 197 (18.78%)	10 / 95 (10.53%)	6 / 70 (8.57%)
occurrences (all)	47	12	6
vomiting			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	20 / 197 (10.15%)	7 / 95 (7.37%)	7 / 70 (10.00%)
occurrences (all)	24	7	8
Hepatobiliary disorders			
hepatic pain			
alternative dictionary used: MedDRA 25.0			

subjects affected / exposed	2 / 197 (1.02%)	0 / 95 (0.00%)	1 / 70 (1.43%)
occurrences (all)	3	0	1
Skin and subcutaneous tissue disorders			
pruritus			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	15 / 197 (7.61%)	5 / 95 (5.26%)	4 / 70 (5.71%)
occurrences (all)	16	5	4
rash			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	14 / 197 (7.11%)	5 / 95 (5.26%)	6 / 70 (8.57%)
occurrences (all)	19	5	8
Renal and urinary disorders			
proteinuria			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	43 / 197 (21.83%)	4 / 95 (4.21%)	22 / 70 (31.43%)
occurrences (all)	74	4	35
Musculoskeletal and connective tissue disorders			
arthralgia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	14 / 197 (7.11%)	5 / 95 (5.26%)	2 / 70 (2.86%)
occurrences (all)	21	7	3
back pain			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	20 / 197 (10.15%)	7 / 95 (7.37%)	3 / 70 (4.29%)
occurrences (all)	23	8	4
Infections and infestations			
pneumonia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	4 / 197 (2.03%)	0 / 95 (0.00%)	4 / 70 (5.71%)
occurrences (all)	4	0	4
urinary tract infection			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	11 / 197 (5.58%)	1 / 95 (1.05%)	2 / 70 (2.86%)
occurrences (all)	18	2	2
Metabolism and nutrition disorders			

decreased appetite			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	49 / 197 (24.87%)	19 / 95 (20.00%)	8 / 70 (11.43%)
occurrences (all)	60	19	8
hyperkalaemia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	13 / 197 (6.60%)	3 / 95 (3.16%)	1 / 70 (1.43%)
occurrences (all)	21	3	1
hypoalbuminaemia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	21 / 197 (10.66%)	4 / 95 (4.21%)	17 / 70 (24.29%)
occurrences (all)	29	4	31
hyponatraemia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	11 / 197 (5.58%)	1 / 95 (1.05%)	5 / 70 (7.14%)
occurrences (all)	16	1	12

Non-serious adverse events	Placebo MEE Cohort	Open Label Ramucirumab + BSC	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 34 (82.35%)	40 / 47 (85.11%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
tumour pain			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
Vascular disorders			
hypertension			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	3 / 34 (8.82%)	11 / 47 (23.40%)	
occurrences (all)	3	16	
General disorders and administration site conditions			
asthenia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	

chills			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 47 (2.13%)	
occurrences (all)	0	2	
fatigue			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	2 / 34 (5.88%)	7 / 47 (14.89%)	
occurrences (all)	2	8	
influenza like illness			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
malaise			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
oedema			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	3 / 47 (6.38%)	
occurrences (all)	0	3	
oedema peripheral			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	2 / 34 (5.88%)	7 / 47 (14.89%)	
occurrences (all)	2	10	
pyrexia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	4 / 34 (11.76%)	3 / 47 (6.38%)	
occurrences (all)	5	3	
Reproductive system and breast disorders			
dysmenorrhoea			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed[1]	0 / 3 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
endometrial hyperplasia			
alternative dictionary used:			

MedDRA 25.0			
subjects affected / exposed[2]	0 / 3 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			
cough			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	5 / 34 (14.71%)	5 / 47 (10.64%)	
occurrences (all)	6	6	
dysphonia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 47 (2.13%)	
occurrences (all)	0	1	
dyspnoea			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	2 / 34 (5.88%)	3 / 47 (6.38%)	
occurrences (all)	2	3	
epistaxis			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	4 / 47 (8.51%)	
occurrences (all)	0	4	
Psychiatric disorders			
insomnia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 34 (2.94%)	3 / 47 (6.38%)	
occurrences (all)	2	3	
Investigations			
alanine aminotransferase increased			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	7 / 34 (20.59%)	2 / 47 (4.26%)	
occurrences (all)	9	3	
aspartate aminotransferase increased			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	9 / 34 (26.47%)	3 / 47 (6.38%)	
occurrences (all)	11	3	
bilirubin conjugated increased			

alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	3 / 34 (8.82%)	1 / 47 (2.13%)	
occurrences (all)	3	1	
blood albumin decreased			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
blood alkaline phosphatase increased			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	2 / 34 (5.88%)	3 / 47 (6.38%)	
occurrences (all)	3	4	
blood bilirubin increased			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	6 / 34 (17.65%)	5 / 47 (10.64%)	
occurrences (all)	12	5	
gamma-glutamyltransferase increased			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	5 / 34 (14.71%)	2 / 47 (4.26%)	
occurrences (all)	6	3	
neutrophil count decreased			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	3 / 34 (8.82%)	1 / 47 (2.13%)	
occurrences (all)	6	2	
platelet count decreased			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	6 / 47 (12.77%)	
occurrences (all)	0	22	
weight decreased			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	3 / 34 (8.82%)	2 / 47 (4.26%)	
occurrences (all)	3	6	
white blood cell count decreased			
alternative dictionary used: MedDRA 25.0			

subjects affected / exposed	2 / 34 (5.88%)	2 / 47 (4.26%)	
occurrences (all)	3	3	
Nervous system disorders			
dizziness			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	3 / 34 (8.82%)	1 / 47 (2.13%)	
occurrences (all)	3	1	
headache			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	1 / 47 (2.13%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	2 / 34 (5.88%)	4 / 47 (8.51%)	
occurrences (all)	2	5	
thrombocytopenia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	3 / 47 (6.38%)	
occurrences (all)	0	3	
Gastrointestinal disorders			
abdominal distension			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	2 / 34 (5.88%)	4 / 47 (8.51%)	
occurrences (all)	2	4	
abdominal pain			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	3 / 34 (8.82%)	4 / 47 (8.51%)	
occurrences (all)	3	4	
abdominal pain upper			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	2 / 34 (5.88%)	3 / 47 (6.38%)	
occurrences (all)	2	3	
ascites			
alternative dictionary used: MedDRA 25.0			

subjects affected / exposed	2 / 34 (5.88%)	6 / 47 (12.77%)	
occurrences (all)	2	6	
constipation			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	3 / 34 (8.82%)	1 / 47 (2.13%)	
occurrences (all)	3	1	
diarrhoea			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	9 / 47 (19.15%)	
occurrences (all)	0	13	
mouth ulceration			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	0 / 47 (0.00%)	
occurrences (all)	0	0	
nausea			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	2 / 34 (5.88%)	6 / 47 (12.77%)	
occurrences (all)	4	6	
vomiting			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	4 / 34 (11.76%)	4 / 47 (8.51%)	
occurrences (all)	4	5	
Hepatobiliary disorders			
hepatic pain			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	3 / 34 (8.82%)	1 / 47 (2.13%)	
occurrences (all)	4	1	
Skin and subcutaneous tissue disorders			
pruritus			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	2 / 34 (5.88%)	3 / 47 (6.38%)	
occurrences (all)	2	3	
rash			
alternative dictionary used: MedDRA 25.0			

subjects affected / exposed	2 / 34 (5.88%)	4 / 47 (8.51%)	
occurrences (all)	2	4	
Renal and urinary disorders			
proteinuria			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	12 / 47 (25.53%)	
occurrences (all)	0	21	
Musculoskeletal and connective tissue disorders			
arthralgia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 34 (2.94%)	3 / 47 (6.38%)	
occurrences (all)	3	3	
back pain			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 34 (0.00%)	2 / 47 (4.26%)	
occurrences (all)	0	2	
Infections and infestations			
pneumonia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 34 (2.94%)	0 / 47 (0.00%)	
occurrences (all)	1	0	
urinary tract infection			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 34 (2.94%)	0 / 47 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
decreased appetite			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	7 / 34 (20.59%)	6 / 47 (12.77%)	
occurrences (all)	7	6	
hyperkalaemia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	2 / 34 (5.88%)	1 / 47 (2.13%)	
occurrences (all)	2	1	
hypoalbuminaemia			

alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	6 / 34 (17.65%)	4 / 47 (8.51%)	
occurrences (all)	7	7	
hyponatraemia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	2 / 34 (5.88%)	4 / 47 (8.51%)	
occurrences (all)	2	7	

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Gender specific events only occurring in male or female participants have had the number of participants at risk adjusted accordingly.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Gender specific events only occurring in male or female participants have had the number of participants at risk adjusted accordingly.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 October 2015	Protocol Amendment (a): - Inclusion Criterion [5] has been modified to allow patients to enter the study if they had a lesion(s) which had previously been treated with locoregional therapy, if the lesion has documented progression after locoregional treatment and is measureable. - Discontinuation criterion has been added if a patient becomes pregnant while on study treatment. - Premedication has been modified to clarify that the premedication with a histamine H1 antagonist is not required to be administered intravenously.
13 May 2016	Protocol Amendment (b): - This amendment included the addition of an interim analysis for unequivocal efficacy, which was conducted when approximately 60% of the planned OS events, at least 191 survival events, had been observed in the ITT population. - Study Completion, was revised to redefine the timing of study completion. Study completion occurred when survival data have been full analyzed. - Pharmacokinetic (PK) and Immunogenicity Analyses, was updated to clarify that limited number of preidentified individuals may gain access to the unblinded PK data at the interim or prior to final database lock in order to initiate the population PK model development for the interim or final analysis. - Exclusion Criterion [17] was revised to clarify that patients who previously had fibrolamellar carcinoma or mixed hepatocellular cholangiocarcinoma are also excluded.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported