



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 | Cyamza,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 full range (min-max) | 57 24 to 80 | 55 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 Not Hispanic or Latino Unknown or Not Reported | 9 58 28 | | |
| Race (NIH/OMB) Units: Subjects | | | |
| American Indian or Alaska Native Asian | 0 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 (\pm 0.201) | -0.099 (\pm 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 \geq 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 occurrences (all) | 19 / 197 (9.64%) 23 | 3 / 95 (3.16%) 3 | 7 / 70 (10.00%) 9 |
| Reproductive system and breast disorders dysmenorrhoea alternative dictionary used: MedDRA 25.0 subjects affected / exposed ^[1] occurrences (all) | 1 / 43 (2.33%) 1 | 0 / 16 (0.00%) 0 | 1 / 15 (6.67%) 1 |
| endometrial hyperplasia alternative dictionary used: MedDRA 25.0 subjects affected / exposed ^[2] occurrences (all) | 1 / 43 (2.33%) 1 | 0 / 16 (0.00%) 0 | 1 / 15 (6.67%) 1 |
| Respiratory, thoracic and mediastinal disorders cough alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) | 21 / 197 (10.66%) 26 | 6 / 95 (6.32%) 7 | 9 / 70 (12.86%) 9 |
| dysphonia alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) | 12 / 197 (6.09%) 12 | 1 / 95 (1.05%) 1 | 1 / 70 (1.43%) 1 |
| dyspnoea alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) | 16 / 197 (8.12%) 19 | 8 / 95 (8.42%) 9 | 0 / 70 (0.00%) 0 |
| epistaxis alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) | 27 / 197 (13.71%) 31 | 3 / 95 (3.16%) 3 | 1 / 70 (1.43%) 2 |
| Psychiatric disorders insomnia alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) | 21 / 197 (10.66%) 24 | 6 / 95 (6.32%) 8 | 5 / 70 (7.14%) 5 |
| Investigations | | | |

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

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

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

| | | | |
|---|-------------------------|------------------------|------------------------|
| decreased appetite alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) | 49 / 197 (24.87%) 60 | 19 / 95 (20.00%) 19 | 8 / 70 (11.43%) 8 |
| hyperkalaemia alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) | 13 / 197 (6.60%) 21 | 3 / 95 (3.16%) 3 | 1 / 70 (1.43%) 1 |
| hypoalbuminaemia alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) | 21 / 197 (10.66%) 29 | 4 / 95 (4.21%) 4 | 17 / 70 (24.29%) 31 |
| hyponatraemia alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) | 11 / 197 (5.58%) 16 | 1 / 95 (1.05%) 1 | 5 / 70 (7.14%) 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 occurrences (all) | 0 / 34 (0.00%) 0 | 0 / 47 (0.00%) 0 | |
| Vascular disorders hypertension alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) | 3 / 34 (8.82%) 3 | 11 / 47 (23.40%) 16 | |
| General disorders and administration site conditions asthenia alternative dictionary used: MedDRA 25.0 subjects affected / exposed occurrences (all) | 0 / 34 (0.00%) 0 | 0 / 47 (0.00%) 0 | |

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

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

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

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

| | | | |
|---|-----------------|----------------|--|
| 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): <ul style="list-style-type: none">- 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): <ul style="list-style-type: none">- 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