



Clinical trial results:

A Phase III randomized, double-blind, placebo-controlled study of sorafenib as adjuvant treatment for hepatocellular carcinoma after surgical resection or local ablation

Summary

| | |
|--------------------------|----------------------------------|
| EudraCT number | 2008-001087-36 |
| Trial protocol | SE GB ES AT BE FR IT PT DE GR BG |
| Global end of trial date | 28 November 2014 |

Results information

| | |
|--------------------------------|---|
| Result version number | v4 (current) |
| This version publication date | 17 February 2019 |
| First version publication date | 24 May 2015 |
| Version creation reason | • Correction of full data set Control of data. |

Trial information

Trial identification

| | |
|-----------------------|------------------|
| Sponsor protocol code | BAY43-9006/12414 |
|-----------------------|------------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00692770 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Bayer AG |
| Sponsor organisation address | Kaiser-Wilhelm-Allee, Leverkusen, Germany, D-51368 |
| Public contact | Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com |
| Scientific contact | Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com |

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 | 27 February 2014 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 29 November 2013 |
| Global end of trial reached? | Yes |
| Global end of trial date | 28 November 2014 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy and safety of sorafenib versus placebo in the adjuvant treatment of hepatocellular carcinoma (HCC) after potentially curative treatment with surgical resection or local ablation.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. A core information and informed consent form was provided. Prior to the beginning of the study, the investigator was required to have the Ethics committee's written approval / favorable opinion of the written informed consent form and any other written information to be provided to subjects. Before entering the study, the informed consent form was read by and explained to all subjects or their legally authorized representative. Each subject had ample opportunity to ask questions and was assured of the right to withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision.

For the collection of images in post-study follow up, the investigator was required to obtain written informed consent from the subject prior to performing any computed tomography / magnetic resonance imaging scan or chest X-ray imaging procedures according to the protocol image acquisition guidelines.

Background therapy: -

Evidence for comparator: -

| | |
|---|----------------|
| Actual start date of recruitment | 15 August 2008 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety |
| Long term follow-up duration | 12 Months |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Portugal: 1 |
| Country: Number of subjects enrolled | Romania: 14 |
| Country: Number of subjects enrolled | Spain: 25 |
| Country: Number of subjects enrolled | Sweden: 7 |
| Country: Number of subjects enrolled | United Kingdom: 9 |
| Country: Number of subjects enrolled | Austria: 17 |
| Country: Number of subjects enrolled | Belgium: 13 |
| Country: Number of subjects enrolled | Bulgaria: 1 |
| Country: Number of subjects enrolled | France: 59 |
| Country: Number of subjects enrolled | Germany: 25 |

| | |
|--------------------------------------|---|
| Country: Number of subjects enrolled | Greece: 1 |
| Country: Number of subjects enrolled | Italy: 146 |
| Country: Number of subjects enrolled | Argentina: 3 |
| Country: Number of subjects enrolled | Brazil: 7 |
| Country: Number of subjects enrolled | Canada: 13 |
| Country: Number of subjects enrolled | Chile: 1 |
| Country: Number of subjects enrolled | Mexico: 5 |
| Country: Number of subjects enrolled | United States: 91 |
| Country: Number of subjects enrolled | Australia: 8 |
| Country: Number of subjects enrolled | China: 256 |
| Country: Number of subjects enrolled | Hong Kong: 31 |
| Country: Number of subjects enrolled | Japan: 149 |
| Country: Number of subjects enrolled | Korea, Democratic People's Republic of: 126 |
| Country: Number of subjects enrolled | New Zealand: 9 |
| Country: Number of subjects enrolled | Singapore: 13 |
| Country: Number of subjects enrolled | Taiwan: 68 |
| Country: Number of subjects enrolled | Switzerland: 5 |
| Country: Number of subjects enrolled | Russian Federation: 11 |
| Worldwide total number of subjects | 1114 |
| EEA total number of subjects | 318 |

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) | 744 |
| From 65 to 84 years | 369 |
| 85 years and over | 1 |

Subject disposition

Recruitment

Recruitment details:

Subject recruitment period was between 15 August 2008 to 12 November 2010.

Pre-assignment

Screening details:

Of 1602 participants who were screened for inclusion in the study, 1114 were enrolled, and 1107 received 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, Monitor, Data analyst, Carer, Assessor |

Arms

| | |
|------------------------------|---------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Sorafenib (Nexavar, BAY43-9006) |

Arm description:

Subjects received 2 tablets of Sorafenib [2*200 milligram (mg)] orally twice daily.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Sorafenib |
| Investigational medicinal product code | BAY43-9006 |
| Other name | Nexavar |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received an oral dose of sorafenib 400 mg tablets (each containing 200 mg) twice daily, on a continuous basis until a criterion for withdrawal was reached. Doses could be interrupted or reduced due to clinically significant toxicities that were considered related to protocol therapy.

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Subjects received 2 tablets of placebo orally twice daily.

| | |
|--|----------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received an oral dose of placebo matching to sorafenib 400 mg tablets (each containing 200 mg) twice daily, on a continuous basis until a criterion for withdrawal was reached. Doses could be interrupted or reduced due to clinically significant toxicities that were considered related to protocol therapy.

| Number of subjects in period 1 | Sorafenib (Nexavar, BAY43-9006) | Placebo |
|--|--|----------------|
| Started | 556 | 558 |
| Study drug administered | 553 | 554 |
| Completed | 82 | 107 |
| Not completed | 474 | 451 |
| Disease progression, recurrence or relapse | 165 | 274 |
| Protocol driven decision point | 3 | - |
| Non-compliant with study medication | 11 | 5 |
| Adverse event | 133 | 41 |
| Radiological and clinical progression | 8 | 8 |
| Consent withdrawn by subject | 93 | 35 |
| Protocol violation | 2 | 7 |
| Randomized but not treated | 3 | 4 |
| Death | 10 | 5 |
| Completed all planned assessments | 35 | 65 |
| Investigator decision not protocol driven | 2 | 1 |
| Lost to follow-up | 7 | 3 |
| Progression by clinical judgment | 2 | 3 |

Baseline characteristics

Reporting groups

| | |
|---|---------------------------------|
| Reporting group title | Sorafenib (Nexavar, BAY43-9006) |
| Reporting group description: | |
| Subjects received 2 tablets of Sorafenib [2*200 milligram (mg)] orally twice daily. | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Subjects received 2 tablets of placebo orally twice daily. | |

| Reporting group values | Sorafenib (Nexavar, BAY43-9006) | Placebo | Total |
|---------------------------------------|---------------------------------|---------|-------|
| Number of subjects | 556 | 558 | 1114 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 383 | 361 | 744 |
| From 65-84 years | 173 | 197 | 370 |
| Age continuous Units: years | | | |
| arithmetic mean | 58.1 | 58.7 | - |
| standard deviation | ± 11.7 | ± 12.2 | |
| Gender categorical Units: Subjects | | | |
| Female | 105 | 97 | 202 |
| Male | 451 | 461 | 912 |

End points

End points reporting groups

| | |
|---|---------------------------------|
| Reporting group title | Sorafenib (Nexavar, BAY43-9006) |
| Reporting group description: | |
| Subjects received 2 tablets of Sorafenib [2*200 milligram (mg)] orally twice daily. | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Subjects received 2 tablets of placebo orally twice daily. | |

Primary: Recurrence Free Survival (RFS) by Independent Assessment

| | |
|--|--|
| End point title | Recurrence Free Survival (RFS) by Independent Assessment |
| End point description: | |
| Disease recurrence of HCC (intra or extra hepatic) was defined as the appearance of a new intrahepatic lesions fulfilling the American Association for the Study of Liver Diseases (AASLD) criteria of diagnosis of HCC or a new extra-hepatic lesions according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria version 1.0. In addition to investigator assessment, all images were reviewed by an independent panel of radiologists. The calculation of the RFS was based on the independent evaluation of the scans. | |
| RFS was defined as the time from randomization to the first documented disease recurrence by independent radiological assessment or death due to any cause whichever occurred first. For subjects who had not recurred or died at the time of analysis, RFS was censored at their last date of evaluable scan before drop-out for any other reason than recurrence or death. | |
| End point type | Primary |
| End point timeframe: | |
| From randomization up to 4 years or until disease recurrence whichever came first | |

| End point values | Sorafenib (Nexavar, BAY43-9006) | Placebo | | |
|----------------------------------|---------------------------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 556 | 558 | | |
| Units: days | | | | |
| median (confidence interval 95%) | 1014 (839 to 1339) | 1026 (841 to 1185) | | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Statistical analysis 1 |
| Comparison groups | Placebo v Sorafenib (Nexavar, BAY43-9006) |

| | |
|---|---------------------------|
| Number of subjects included in analysis | 1114 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.258329 ^[1] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.94 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.78 |
| upper limit | 1.134 |

Notes:

[1] - One sided P-value was stratified by region, risk of recurrence and previous curative treatment.

Secondary: Time to Recurrence (TTR) by Independent Assessment

| | |
|--|--|
| End point title | Time to Recurrence (TTR) by Independent Assessment |
| End point description: | |
| TTR was defined as the time from randomization to the first documented disease recurrence by independent radiological assessment. For subjects who had not recurred at the time of analysis, TTR was censored at their last date of evaluable scan before withdrawal for any other reason than recurrence. '99999' in the reported data indicates value could not be estimated due to censored data. | |
| End point type | Secondary |
| End point timeframe: | |
| From randomization up to 4 years or until disease recurrence whichever came first | |

| End point values | Sorafenib (Nexavar, BAY43-9006) | Placebo | | |
|----------------------------------|---------------------------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 556 | 558 | | |
| Units: days | | | | |
| median (confidence interval 95%) | 1172 (924 to 99999) | 1089 (923 to 1260) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Statistical analysis 1 |
| Comparison groups | Sorafenib (Nexavar, BAY43-9006) v Placebo |
| Number of subjects included in analysis | 1114 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.121383 ^[2] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.891 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.735 |
| upper limit | 1.081 |

Notes:

[2] - One-sided P-value was stratified by region, risk of recurrence and previous curative treatment

Secondary: Overall Survival (OS)

| | |
|-----------------|-----------------------|
| End point title | Overall Survival (OS) |
|-----------------|-----------------------|

End point description:

OS was defined as the time from randomization to date of death due to any cause. OS for subjects alive at the time of analysis was censored at their last date of contact. '99999' in the reported data indicates value could not be estimated due to censored data.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From randomization of the first subject until 4 years later.

| End point values | Sorafenib (Nexavar, BAY43-9006) | Placebo | | |
|----------------------------------|---------------------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 556 | 558 | | |
| Units: days | | | | |
| median (confidence interval 95%) | 99999 (99999 to 99999) | 99999 (99999 to 99999) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Statistical analysis 1 |
| Comparison groups | Sorafenib (Nexavar, BAY43-9006) v Placebo |
| Number of subjects included in analysis | 1114 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.484742 ^[3] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.995 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.761 |
| upper limit | 1.3 |

Notes:

[3] - One-sided P-value was stratified by region, risk of recurrence and previous curative treatment

Other pre-specified: Patient Reported Outcomes: Euroqol-5 Dimensions (EQ-5D) -

Index Score

| | |
|-----------------|---|
| End point title | Patient Reported Outcomes: Euroqol-5 Dimensions (EQ-5D) - Index Score |
|-----------------|---|

End point description:

The EQ-5D is a generic quality of life preference based on a validated instrument used in cancer and in general population, with 2 parts: Index and Visual Analogue Scale. The EQ-5D Index is a descriptive system of the following health dimensions: mobility, selfcare, usual activities, pain/discomfort, and anxiety/depression. Subjects were asked to choose any one of the 3 response levels for each dimension: no problems, some problems, and severe problems. The 5 health dimensions were summarized into a single score, the EQ-5D Index score which ranged from -0.59 to 1 with higher scores representing better health states (0=death, 1= perfect health, and -0.59=a health state worse than death). A change of at least 0.10 to 0.12 points was considered a minimally important difference using Eastern Cooperative Oncology Group Performance Status as the anchor. The results on the Analysis of covariance of time-adjusted Area under curve for the EQ-5D index score were reported.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Cycle (C) Day (D)1, C2D1, C3D1 and subsequent cycles up to C18, end of intervention visit (1 to 2 weeks after last dose)

| End point values | Sorafenib (Nexavar, BAY43-9006) | Placebo | | |
|--|---------------------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 556 | 558 | | |
| Units: unit on a scale | | | | |
| least squares mean (confidence interval 95%) | 0.827 (0.804 to 0.85) | 0.866 (0.843 to 0.888) | | |

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

An analysis of covariance (ANCOVA) model was used to estimate the mean difference in the time-adjusted Area Under Curve (AUC) between the two treatment groups, with covariates for baseline scores and stratification factors. To test the treatment effect, a mixed linear model (random coefficient model) was used for the EQ-5D index score. Statistical tests were performed with a 2 sided type I error of 5%.

| | |
|---|---|
| Comparison groups | Sorafenib (Nexavar, BAY43-9006) v Placebo |
| Number of subjects included in analysis | 1114 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | Mean difference |
| Point estimate | 0.039 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.025 |
| upper limit | 0.052 |

Other pre-specified: Patient Reported Outcomes: Euroqol-5 Dimensions (EQ-5D) - Visual Analogue Scale (VAS) Score

| | |
|-----------------|---|
| End point title | Patient Reported Outcomes: Euroqol-5 Dimensions (EQ-5D) - Visual Analogue Scale (VAS) Score |
|-----------------|---|

End point description:

The EQ-5D is a generic quality of life preference based on a validated instrument used in cancer and in general population, with 2 parts: Index and Visual Analogue Scale. The EQ-5D VAS is a measure that represents health status as a single value. It is a 20-centimetre vertical graduated visual analogue scale with scores that ranged from 0 (worst imaginable health state) to 100 (best imaginable health state). The respondent rated his/her current health state by drawing a line from the box marked 'your own health state today' to the appropriate point on the EQ-5D VAS. A 3-digit number (including leading zeros) was read off the scale from the point where the respondent's line crossed the scale, which was the EQ-5D VAS score. A change of at least 7 points on the VAS was considered as minimally important. The results on the ANCOVA analysis of time-adjusted AUC for the EQ-5D VAS score were reported.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Cycle (C) Day (D)1, C2D1, C3D1 and subsequent cycles up to C18, end of intervention visit (1 to 2 weeks after last dose)

| | | | | |
|--|---------------------------------|---------------------------|--|--|
| End point values | Sorafenib (Nexavar, BAY43-9006) | Placebo | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 556 | 558 | | |
| Units: unit on a scale | | | | |
| least squares mean (confidence interval 95%) | 77.203 (75.184 to 79.223) | 80.181 (78.212 to 82.151) | | |

Statistical analyses

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 1 |
|-----------------------------------|------------------------|

Statistical analysis description:

An analysis of covariance (ANCOVA) model was used to estimate the mean difference in the time-adjusted Area Under Curve (AUC) between the two treatment groups, with covariates for baseline scores and stratification factors. To test the treatment effect, a mixed linear model (random coefficient model) was used for the EQ-5D VAS score. Statistical tests were performed with a 2 sided type I error of 5%.

| | |
|---|---|
| Comparison groups | Sorafenib (Nexavar, BAY43-9006) v Placebo |
| Number of subjects included in analysis | 1114 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | Mean difference |
| Point estimate | 2.978 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.797 |
| upper limit | 4.159 |

Other pre-specified: Patient Reported Outcomes: Functional Assessment of Cancer Therapy (FACT)-Hepatobiliary Subscale (HEP) Score

| | |
|-----------------|--|
| End point title | Patient Reported Outcomes: Functional Assessment of Cancer Therapy (FACT)-Hepatobiliary Subscale (HEP) Score |
|-----------------|--|

End point description:

The FACT-HEP is a 45 item, self-administered, multi-dimensional, psychometrically sound questionnaire used extensively in oncology clinical trials. FACT-HEP consisted of five subscales: Physical Well-Being (PWB), Social Well-Being (SWB), Emotional Well-Being (EWB), Functional Well-Being (FWB), and Hepatobiliary Cancer Subscale (HCS). The PWB, FWB, SWB and EWB were summed to form the FACT-General (FACT-G) total score. The FACT-G and HCS scores were summed to form the FACT-HEP total score. FACT-HEP scores ranged from 0 to 180 and the higher scores represented a better quality of life. Subjects responded to each item on a 5-point Likert-type scale ranging from 0 (not at all) to 4 (very much). The minimally important difference (MID) for the FACT-Hep total score was in the range of 8 to 9. The results on the ANCOVA analysis of time-adjusted AUC for the FACT-HEP score were reported.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Cycle (C) Day (D)1, C2D1, C3D1 and subsequent cycles up to C18, end of intervention visit (1 to 2 weeks after last dose)

| End point values | Sorafenib (Nexavar, BAY43-9006) | Placebo | | |
|--|---------------------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 556 | 558 | | |
| Units: unit on a scale` | | | | |
| least squares mean (confidence interval 95%) | 138.7 (135.9 to 141.5) | 143.79 (141.1 to 146.5) | | |

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

An ANCOVA model was used to estimate the mean difference in the time-adjusted AUC between the two treatment groups, with covariates for baseline scores and stratification factors. To test the treatment effect, a mixed linear model (random coefficient model) was used for the FACT-HEP score. Statistical tests were performed with a 2 sided type I error of 5%.

| | |
|-------------------|---|
| Comparison groups | Sorafenib (Nexavar, BAY43-9006) v Placebo |
|-------------------|---|

| | |
|---|-----------------|
| Number of subjects included in analysis | 1114 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | Mean difference |
| Point estimate | 5.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 3.5 |
| upper limit | 6.7 |

Other pre-specified: Patient Reported Outcomes: Functional Assessment of Cancer Therapy (FACT)-General (G) Total Score

| | |
|-----------------|---|
| End point title | Patient Reported Outcomes: Functional Assessment of Cancer Therapy (FACT)-General (G) Total Score |
|-----------------|---|

End point description:

The PWB, FWB, SWB and EWB were summed to form the FACT-G total score. Subjects responded to each item on a 5-point Likert-type scale ranging from 0 (not at all) to 4 (very much). FACT-G scores ranged from 0 to 108 and the higher scores represented a better quality of life. The MID for the FACT-G total score was in the range of 6 to 7. The results on the ANCOVA analysis of time-adjusted AUC for the FACT-G score were reported.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Cycle (C) Day (D)1, C2D1, C3D1 and subsequent cycles up to C18, end of intervention visit (1 to 2 weeks after last dose)

| End point values | Sorafenib (Nexavar, BAY43-9006) | Placebo | | |
|--|---------------------------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 556 | 558 | | |
| Units: unit on a scale | | | | |
| least squares mean (confidence interval 95%) | 80.46 (78.6 to 82.3) | 82.95 (81.1 to 84.8) | | |

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

An ANCOVA model was used to estimate the mean difference in the time-adjusted AUC between the two treatment groups, with covariates for baseline scores and stratification factors. To test the treatment effect, a mixed linear model (random coefficient model) was used for the FACT-G score. Statistical tests were performed with a 2 sided type I error of 5%.

| | |
|-------------------|---|
| Comparison groups | Sorafenib (Nexavar, BAY43-9006) v Placebo |
|-------------------|---|

| | |
|---|-----------------|
| Number of subjects included in analysis | 1114 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | Mean difference |
| Point estimate | 2.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.4 |
| upper limit | 3.6 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

After the subject has signed the informed consent, up to 30 days post treatment discontinuation

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 17.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Subjects received 2 tablets of placebo orally twice daily.

| | |
|-----------------------|---------------------------------|
| Reporting group title | Sorafenib (Nexavar, BAY43-9006) |
|-----------------------|---------------------------------|

Reporting group description:

Subjects received 2 tablets of Sorafenib [2*200 milligram (mg)] orally twice daily.

| Serious adverse events | Placebo | Sorafenib (Nexavar, BAY43-9006) | |
|---|--------------------|---------------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 230 / 548 (41.97%) | 228 / 559 (40.79%) | |
| number of deaths (all causes) | 131 | 114 | |
| number of deaths resulting from adverse events | 9 | 15 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Benign hepatic neoplasm | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bladder cancer | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Breast cancer | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic myeloid leukaemia | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colon cancer | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric cancer | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemangioma of liver | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic neoplasm | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Laryngeal squamous cell carcinoma | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to lung | | | |
| subjects affected / exposed | 2 / 548 (0.36%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastatic pain | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Non-Hodgkin's lymphoma | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Oesophageal adenocarcinoma | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pancreatic carcinoma | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal adenocarcinoma | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Schwannoma | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin papilloma | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Squamous cell carcinoma of the hypopharynx | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Adenocarcinoma pancreas | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung neoplasm malignant | | | |
| subjects affected / exposed | 2 / 548 (0.36%) | 4 / 559 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 4 | 1 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Desmoid tumour | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostate cancer | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary neoplasm | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nasopharyngeal cancer | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lip and/or oral cavity cancer | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neoplasm recurrence | | | |
| subjects affected / exposed | 2 / 548 (0.36%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung neoplasm | | | |

| | | | |
|---|--------------------|-------------------|--|
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Huerthle cell carcinoma | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oral papilloma | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatocellular carcinoma | | | |
| subjects affected / exposed | 130 / 548 (23.72%) | 82 / 559 (14.67%) | |
| occurrences causally related to treatment / all | 0 / 154 | 0 / 98 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Vascular disorders | | | |
| Arteriovenous fistula | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 2 / 559 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral vascular disorder | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Inferior vena caval occlusion | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral embolism | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Artery dissection | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral arterial occlusive disease | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Incisional hernia repair | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neoplasm prophylaxis | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Removal of foreign body from gastrointestinal tract | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Chest pain | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 2 / 559 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Death | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Drowning | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 3 / 559 (0.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 4 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multi-organ failure | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 3 / 559 (0.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 3 | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sudden cardiac death | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Coronary artery restenosis | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Inflammation | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Unevaluable event | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Benign prostatic hyperplasia | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 2 / 559 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemoptysis | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Interstitial lung disease | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Laryngeal oedema | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 3 / 559 (0.54%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleurisy | | | |
| subjects affected / exposed | 2 / 548 (0.36%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonitis | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 4 / 548 (0.73%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 5 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary granuloma | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 2 / 559 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary haemorrhage | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary mass | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 2 / 559 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinusitis noninfective | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Alcohol abuse | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Alcoholism | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Confusional state | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 2 / 559 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 2 / 559 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Lipase increased | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Liver function test abnormal | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 2 / 559 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Accidental overdose | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arterial injury | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Humerus fracture | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Incisional hernia | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 2 / 559 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Ligament sprain | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Radius fracture | | | |
| subjects affected / exposed | 3 / 548 (0.55%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal compression fracture | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sternal fracture | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tibia fracture | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ulna fracture | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular injury | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wrist fracture | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thoracic vertebral fracture | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Face injury | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Brain contusion | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound evisceration | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural bile leak | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pelvic fracture | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Limb crushing injury | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Toxicity to various agents | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 2 / 559 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Angina pectoris | | | |
| subjects affected / exposed | 2 / 548 (0.36%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 1 / 3 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina unstable | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aortic valve stenosis | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arteriosclerosis coronary artery | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 2 / 559 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrioventricular block complete | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Bradycardia | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery disease | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 2 / 559 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 2 / 559 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Left ventricular dysfunction | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 2 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Carotid artery thrombosis | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebellar haemorrhage | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral haemorrhage | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 548 (0.18%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 1 / 1 | |
| Cerebral infarction | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 2 / 559 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral ischaemia | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 2 / 559 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Encephalopathy | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 3 / 559 (0.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Guillain-Barre syndrome | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 2 / 559 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Headache | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic encephalopathy | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 548 (0.36%) | 3 / 559 (0.54%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertensive encephalopathy | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Presyncope | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal cord compression | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal cord infarction | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancytopenia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bone marrow failure | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Deafness | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tinnitus | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vertigo | | | |
| subjects affected / exposed | 2 / 548 (0.36%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 4 / 559 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Retinal vein occlusion | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 3 / 559 (0.54%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ascites | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 3 / 559 (0.54%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Crohn's disease | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diaphragmatic hernia, obstructive | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 548 (0.36%) | 2 / 559 (0.36%) | |
| occurrences causally related to treatment / all | 1 / 3 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Duodenal ulcer | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Duodenitis | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enteritis | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femoral hernia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric ulcer haemorrhage | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 4 / 559 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematemesis | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Impaired gastric emptying | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Inguinal hernia | | | |
| subjects affected / exposed | 3 / 548 (0.55%) | 2 / 559 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestine perforation | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophageal varices haemorrhage | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 548 (0.00%) | 4 / 559 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 2 / 559 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis acute | | | |
| subjects affected / exposed | 2 / 548 (0.36%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Umbilical hernia | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 2 / 548 (0.36%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric volvulus | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhoidal haemorrhage | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 548 (0.18%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Varices oesophageal | | | |
| subjects affected / exposed | 2 / 548 (0.36%) | 2 / 559 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric varices haemorrhage | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal hernia | | | |
| subjects affected / exposed | 2 / 548 (0.36%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Localised intraabdominal fluid collection | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Bile duct stone | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Biliary fistula | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholangitis | | | |
| subjects affected / exposed | 2 / 548 (0.36%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholangitis acute | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 2 / 559 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic failure | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hepatic function abnormal | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 4 / 559 (0.72%) | |
| occurrences causally related to treatment / all | 2 / 2 | 9 / 9 | |
| deaths causally related to treatment / all | 0 / 0 | 3 / 3 | |
| Hepatorenal syndrome | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Jaundice cholestatic | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Portal vein thrombosis | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 2 / 559 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 4 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bile duct stenosis | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic mass | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Biloma | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Liver injury | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 2 / 559 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Angioedema | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dermal cyst | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dermatitis allergic | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Palmar-plantar erythrodysaesthesia syndrome | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 10 / 559 (1.79%) | |
| occurrences causally related to treatment / all | 1 / 1 | 11 / 11 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pruritus | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rash | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 2 / 559 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin ulcer | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Telangiectasia | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Calculus urinary | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 2 / 559 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hydronephrosis | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 2 / 548 (0.36%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nephrotic syndrome | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal colic | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Renal failure acute | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 2 / 559 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ureteric obstruction | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary retention | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetic nephropathy | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bone formation increased | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Exostosis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gouty arthritis | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteoarthritis | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rotator cuff syndrome | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 16 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 2 / 548 (0.36%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spondylolisthesis | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bacteraemia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 3 / 559 (0.54%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal infection | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatitis B | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Hepatitis C | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Liver abscess | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteomyelitis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peritonitis | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 2 / 559 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary tuberculosis | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 2 / 548 (0.36%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Superinfection | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tuberculosis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 2 / 559 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urosepsis | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal abscess | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal bacteraemia | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Biliary sepsis | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute hepatitis B | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Abdominal abscess | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 3 / 548 (0.55%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung infection | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peritonitis bacterial | | | |
| subjects affected / exposed | 1 / 548 (0.18%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infected dermal cyst | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infectious pleural effusion | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 2 / 548 (0.36%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoglycaemia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 548 (0.36%) | 0 / 559 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Type 2 diabetes mellitus | | | |
| subjects affected / exposed | 0 / 548 (0.00%) | 1 / 559 (0.18%) | |
| 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 | Placebo | Sorafenib (Nexavar, BAY43-9006) | |
|---|--------------------|---------------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 360 / 548 (65.69%) | 522 / 559 (93.38%) | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 38 / 548 (6.93%) | 54 / 559 (9.66%) | |
| occurrences (all) | 177 | 251 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 35 / 548 (6.39%) | 51 / 559 (9.12%) | |
| occurrences (all) | 188 | 226 | |
| Platelet count decreased | | | |
| subjects affected / exposed | 26 / 548 (4.74%) | 48 / 559 (8.59%) | |
| occurrences (all) | 202 | 300 | |
| Weight decreased | | | |
| subjects affected / exposed | 13 / 548 (2.37%) | 60 / 559 (10.73%) | |
| occurrences (all) | 41 | 254 | |

| | | | |
|--|--|---|--|
| Weight increased subjects affected / exposed occurrences (all) | 42 / 548 (7.66%) 310 | 14 / 559 (2.50%) 68 | |
| Vascular disorders Hypertension subjects affected / exposed occurrences (all) | 65 / 548 (11.86%) 331 | 142 / 559 (25.40%) 869 | |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 33 / 548 (6.02%) 108 | 40 / 559 (7.16%) 111 | |
| Blood and lymphatic system disorders Thrombocytopenia subjects affected / exposed occurrences (all) | 14 / 548 (2.55%) 97 | 29 / 559 (5.19%) 217 | |
| General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all) | 66 / 548 (12.04%) 300 24 / 548 (4.38%) 32 | 83 / 559 (14.85%) 315 33 / 559 (5.90%) 39 | |
| Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Ascites subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Diarrhoea | 46 / 548 (8.39%) 115 14 / 548 (2.55%) 36 19 / 548 (3.47%) 67 36 / 548 (6.57%) 122 | 55 / 559 (9.84%) 156 28 / 559 (5.01%) 75 39 / 559 (6.98%) 145 41 / 559 (7.33%) 105 | |

| | | | |
|---|-------------------|--------------------|--|
| subjects affected / exposed | 64 / 548 (11.68%) | 242 / 559 (43.29%) | |
| occurrences (all) | 186 | 1201 | |
| Dyspepsia | | | |
| subjects affected / exposed | 30 / 548 (5.47%) | 20 / 559 (3.58%) | |
| occurrences (all) | 125 | 112 | |
| Nausea | | | |
| subjects affected / exposed | 24 / 548 (4.38%) | 50 / 559 (8.94%) | |
| occurrences (all) | 45 | 119 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 44 / 548 (8.03%) | 30 / 559 (5.37%) | |
| occurrences (all) | 116 | 76 | |
| Dysphonia | | | |
| subjects affected / exposed | 3 / 548 (0.55%) | 41 / 559 (7.33%) | |
| occurrences (all) | 7 | 133 | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 18 / 548 (3.28%) | 187 / 559 (33.45%) | |
| occurrences (all) | 65 | 750 | |
| Palmar-plantar erythrodysesthesia syndrome | | | |
| subjects affected / exposed | 27 / 548 (4.93%) | 390 / 559 (69.77%) | |
| occurrences (all) | 139 | 2196 | |
| Pruritus | | | |
| subjects affected / exposed | 58 / 548 (10.58%) | 47 / 559 (8.41%) | |
| occurrences (all) | 263 | 133 | |
| Rash | | | |
| subjects affected / exposed | 45 / 548 (8.21%) | 95 / 559 (16.99%) | |
| occurrences (all) | 126 | 296 | |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 31 / 548 (5.66%) | 24 / 559 (4.29%) | |
| occurrences (all) | 178 | 111 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |

| | | | |
|--|-------------------------|-------------------------|--|
| subjects affected / exposed occurrences (all) | 30 / 548 (5.47%) 139 | 34 / 559 (6.08%) 162 | |
| Back pain subjects affected / exposed occurrences (all) | 37 / 548 (6.75%) 192 | 43 / 559 (7.69%) 152 | |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) | 38 / 548 (6.93%) 69 | 30 / 559 (5.37%) 66 | |
| Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) | 18 / 548 (3.28%) 52 | 40 / 559 (7.16%) 104 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 26 May 2008 | Amendment 1 dated 26 MAY 2008 (IND modification serial number 2656) <ul style="list-style-type: none">- Removed tumor block sampling- Minor clarifications of inclusion and exclusion criteria- Added PK sampling- Clarified that randomization codes for investigators or pharmacists would be managed by the IVRS system- Clarified end of post study follow-up- Clarified study medication storage conditions |
| 12 June 2008 | Amendment 2 (local amendment for Japan), dated 12 JUN 2008 <ul style="list-style-type: none">- Japan specific changes with regard to AE monitoring, SAEs, unexpected AEs, ethics committees, identity of investigational products and premature termination of the study/closure of a center. |
| 01 May 2009 | Amendment 3 dated 1 MAY 2009 (IND modification serial number 2776) <ul style="list-style-type: none">- Increased cap for Asia Pacific patients from 450 to 550 patients allowing a balanced enrollment compared with Western patients while taking into account the higher prevalence of HCC patients in the Asia Pacific region compared with the rest of the world.- Clarified timing definitions for inclusion/exclusion criteria- Clarified exclusion criteria definition regarding potential transplant patients- Clarified study medication storage conditions for blister pack used in the Asia Pacific region- Amended criteria for serious adverse events (SAE) reporting in case of hospitalization in line with updated procedures |
| 02 October 2009 | Amendment 4 dated 2 OCT 2009 (IND modification serial number 2805) <ul style="list-style-type: none">- Expanded time window for time from surgery/ablation to eligibility CT or MRI scan: The additional time beyond the targeted 4 weeks from curative treatment to eligibility scan was expanded to ensure maximum recovery time from curative treatment, while maintaining a short enough timeframe from curative treatment to commencing adjuvant treatment to derive maximum adjuvant treatment benefit. The minimum time of 3 weeks (21 days) was maintained to ensure a valid assessment of the remission status.- Clarified ablation definitions to allow a combination of percutaneous ethanol injection (PEI) and percutaneous or intraoperative radiofrequency ablation (RFA) |
| 11 February 2010 | Amendment 5 dated 11 FEB 2010 (IND modification serial number 2870) <ul style="list-style-type: none">- Removed Asia Pacific cap: This was done in order to allow completely competitive enrolment across all geographical regions. This was decided based on a blinded inspection of patients' safety profiles, treatment duration, and frequency of discontinuation that did not reveal any unexpected issues or concerns and confirmed that no relevant differences regarding these parameters could be observed across geographical regions. It was therefore considered appropriate to allow complete competitive enrolment into the study and to remove the predefined recruitment cap on the Asia-Pacific region. In addition, it was thought that this would allow a representative ethnical distribution across the regions. It was further considered that despite removing the cap on Asian patients, that the large overall sample size of 1100 subjects would still allow a sufficiently large number of Western patients, which was expected to be greater than 400 subjects. |

| | |
|-----------------|---|
| 26 January 2011 | Amendment 6 dated 26 JAN 2011 (for all countries other than the USA) (IND modification serial number 2999) - Allowed the continuation of collection of CT/MRI scans beyond premature termination of treatment, into the Post Study Follow Up - Statistical section was modified to state that recurrence events observed from scans collected during post study follow up would be used in the primary analysis. This was done because it was thought that the additional scan evaluations collected post study would reduce the censoring rate and therefore reduce the possibility of biasing the results of the primary endpoint. |
| 31 May 2011 | Amendment 8 dated 31 MAY 2011 (for USA only) (IND modification serial number 3033) - Following feedback from FDA regarding protocol amendment 6, this amendment stated that recurrence events observed from scans collected during post study follow up would not be used in the primary analysis. This data would be used for supportive sensitivity analyses only. |
| 31 May 2011 | Amendment 9 dated 31 MAY 2011 (for all countries other than the USA) - Following feedback from FDA regarding protocol amendment 6, this amendment stated that recurrence events observed from scans collected during post study follow up would not be used in the primary analysis. This data would be used for supportive sensitivity analyses only. |
| 20 June 2012 | Amendment 10, dated 20 JUN 2012 (applicable to all countries) (IND modification serial number 3120) - Power of the primary end point reduced from 90% to 80%, thereby reducing the number of centrally confirmed recurrences required from 611 to 457. It was decided that this change would shorten the duration of the study and thereby reduce the amount of missing data due to patient drop-outs. - Clarification was included, stating that 4 years was equal to 204 weeks and that patients who reached 4 years on treatment would continue to be followed for recurrence during follow up. CT/MRI scans were to be performed every 6 months per study image acquisition guidelines. Any recurrences observed in this group of patients could then be included in the primary analysis. - For patients who discontinued treatment prematurely and continued scan collection during follow up (according to amendment 6), the frequency of scan collection was to decrease from 3 monthly to 6 monthly once the patient reached their date of randomization + 204 weeks. Recurrences observed during follow up for patients who withdrew prematurely from treatment (per protocol amendment 6) were still not to be included in the primary analysis (per amendments 8 and 9). |
| 06 August 2012 | Amendment 11, dated 6 AUG 2012 (applicable to all countries) (IND modification serial number 3120) - Administrative only - corrects inconsistency within protocol amendment 10 |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Decimal places were automatically truncated if last decimal equals zero.

Notes: