



Clinical trial results:

A Randomized, Double-blind, Multi-center Phase III Study of Brivanib versus Sorafenib as First-line Treatment in Patients with Advanced Hepatocellular Carcinoma (The BRISK FL Study)

Summary

| | |
|--------------------------|-------------------------|
| EudraCT number | 2008-003533-24 |
| Trial protocol | ES FR DE SE BE GB IT CZ |
| Global end of trial date | 26 September 2013 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 23 December 2016 |
| First version publication date | 23 December 2016 |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | CA182-033 |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00858871 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Bristol-Myers Squibb |
| Sponsor organisation address | Chausée de la Hulpe 185, Brussels, Belgium, 1170 |
| Public contact | Bristol-Myers Squibb Study Director, Bristol-Myers Squibb International Corporation, clinical.trials@bms.com |
| Scientific contact | Bristol-Myers Squibb Study Director, Bristol-Myers Squibb International Corporation, clinical.trials@bms.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 | 26 September 2013 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 26 September 2013 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to compare the Overall Survival (OS) of brivanib versus sorafenib in subjects with advanced HCC who have not received prior systemic treatment.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator:

Sorafenib was the first and only systemic therapy proven to confer a survival benefit in advanced/unresectable Hepatocellular Carcinoma (HCC). Sorafenib was administered at a dose of 400 mg twice daily (BID). It was approved by Food and Drug Administration (FDA), European Medicines Agency (EMA) and many other countries' health authorities for the treatment of HCC.

| | |
|---|------------------|
| Actual start date of recruitment | 19 May 2009 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy |
| Long term follow-up duration | 46 Months |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------------|
| Country: Number of subjects enrolled | Argentina: 11 |
| Country: Number of subjects enrolled | Australia: 15 |
| Country: Number of subjects enrolled | Brazil: 124 |
| Country: Number of subjects enrolled | Canada: 22 |
| Country: Number of subjects enrolled | Hong Kong: 39 |
| Country: Number of subjects enrolled | India: 97 |
| Country: Number of subjects enrolled | Japan: 146 |
| Country: Number of subjects enrolled | Korea, Republic of: 178 |
| Country: Number of subjects enrolled | Mexico: 54 |
| Country: Number of subjects enrolled | China: 249 |
| Country: Number of subjects enrolled | Puerto Rico: 1 |
| Country: Number of subjects enrolled | Russian Federation: 42 |
| Country: Number of subjects enrolled | South Africa: 15 |
| Country: Number of subjects enrolled | Taiwan: 204 |
| Country: Number of subjects enrolled | Thailand: 59 |

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Turkey: 21 |
| Country: Number of subjects enrolled | United States: 51 |
| Country: Number of subjects enrolled | Poland: 26 |
| Country: Number of subjects enrolled | Spain: 6 |
| Country: Number of subjects enrolled | Sweden: 7 |
| Country: Number of subjects enrolled | United Kingdom: 66 |
| Country: Number of subjects enrolled | Belgium: 1 |
| Country: Number of subjects enrolled | Czech Republic: 28 |
| Country: Number of subjects enrolled | France: 136 |
| Country: Number of subjects enrolled | Germany: 28 |
| Country: Number of subjects enrolled | Italy: 39 |
| Worldwide total number of subjects | 1665 |
| EEA total number of subjects | 337 |

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) | 1025 |
| From 65 to 84 years | 632 |
| 85 years and over | 8 |

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 168 sites in 26 countries.

Pre-assignment

Screening details:

A total of 1665 subjects were enrolled and 1155 were randomised. Reasons for 510 subjects not randomised were: 5 adverse event, 29 subject withdrew consent, 2 death, 7 lost to follow-up, 458 subjects no longer met study criteria, and 10 other reasons. 1150 subjects were treated.

Period 1

| | |
|------------------------------|---------------------------------------|
| Period 1 title | Treatment Period |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Carer |

Blinding implementation details:

To maintain blinding of study treatment, study drugs were prepared in a double-dummy design using placebo matching the active treatments.

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|------------------|-----------|
| Arm title | Sorafenib |
|------------------|-----------|

Arm description:

Subjects received sorafenib orally (400 mg BID) and brivanib alaninate orally matched placebo once daily (QD). Sorafenib was administered as 2*200-mg capsules in the AM and 2*200-mg capsules in the PM.

| | |
|--|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Sorafenib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects were administered 400 mg of sorafenib capsules orally BID, 2*200-mg capsules in the AM and 2*200-mg capsules in the PM. Sorafenib was provided as gray, opaque, capsule shells.

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

Dosage and administration details:

Subjects were administered four placebo matching brivanib alaninate tablets orally QD. Placebo brivanib alaninate tablets were provided as plain, white, biconvex, oval shaped film-coated tablets.

| | |
|------------------|----------|
| Arm title | Brivanib |
|------------------|----------|

Arm description:

Subjects received brivanib alaninate orally (800 mg QD) and sorafenib orally matched placebo BID. Brivanib alaninate was administered as 4*200-mg tablets and sorafenib matched placebo as 2*200-mg capsules in the AM and 2*200-mg capsules in the PM.

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|--------------------|
| Investigational medicinal product name | Brivanib alaninate |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects were administered 800 mg brivanib alaninate tablets (4*200 mg tablets) orally QD. Brivanib alaninate tablets were provided as plain, white, biconvex, oval shaped film-coated tablets.

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

Dosage and administration details:

Subjects were administered four placebo matched sorafenib capsules orally BID, 2 capsules in the AM and 2 capsules in the PM. Sorafenib matched placebo was provided as gray, opaque, capsule shells.

| Number of subjects in period 1^[1] | Sorafenib | Brivanib |
|---|-----------|----------|
| Started | 578 | 577 |
| Treated | 575 | 575 |
| Completed | 62 | 35 |
| Not completed | 516 | 542 |
| Consent withdrawn by subject | 6 | 7 |
| Not Reported | - | 2 |
| Death | 4 | 1 |
| Other | 4 | 2 |
| Maximum Clinical Benefit | 2 | 4 |
| Adverse Event Unrelated to Study Drug | 54 | 63 |
| Subject No Longer Meets Study Criteria | 3 | 2 |
| Poor/Non-compliance | 2 | - |
| Study Drug Toxicity | 85 | 139 |
| Subject Request to Discontinue Study Treatment | 50 | 52 |
| Lost to follow-up | 1 | 2 |
| Disease Progression | 305 | 268 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The number of subjects reported in the baseline period are different from the worldwide number enrolled in the trial, as out of 1665 subjects enrolled, only 1155 were randomised and treated. 510 subjects did not participate in the treatment period due to various reasons.

Period 2

| | |
|------------------------------|---------------------------------------|
| Period 2 title | Follow-up Period |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Carer |

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|------------------|-----------|
| Arm title | Sorafenib |
|------------------|-----------|

Arm description:

Subjects received sorafenib orally (400 mg BID) and brivanib alaninate orally matched placebo QD in the treatment period. No treatment was received in the follow-up.

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

Dosage and administration details:

No treatment was received in the follow-up, however, subjects were administered four placebo matching brivanib alaninate tablets orally QD in the treatment period.

| | |
|--|-----------|
| Investigational medicinal product name | Sorafenib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

No treatment was received in the follow-up period, however, subjects were administered 400 mg of sorafenib capsules orally twice a day (BID) in the treatment period.

| | |
|------------------|----------|
| Arm title | Brivanib |
|------------------|----------|

Arm description:

Subjects received brivanib alaninate orally (800 mg QD) and sorafenib orally matched placebo BID in the treatment period. No treatment was received in the follow-up.

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

Dosage and administration details:

No treatment was received in the follow-up. Subjects were administered four placebo matched sorafenib capsules orally BID in the treatment period.

| | |
|--|--------------------|
| Investigational medicinal product name | Brivanib alaninate |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

No treatment was received in the follow-up, however, subjects were administered 800 mg brivanib alaninate tablets (4*200 mg tablets) orally QD in the treatment period.

| Number of subjects in period 2 | Sorafenib | Brivanib |
|---------------------------------------|-----------|----------|
| Started | 62 | 35 |
| Completed | 92 | 108 |
| Not completed | 351 | 365 |
| Consent withdrawn by subject | 4 | 5 |
| Death | 344 | 358 |
| Other | 1 | 1 |
| Lost to follow-up | 2 | 1 |
| Joined | 381 | 438 |
| Rejoined for follow-up | 381 | 438 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | Sorafenib |
|-----------------------|-----------|

Reporting group description:

Subjects received sorafenib orally (400 mg BID) and brivanib alaninate orally matched placebo once daily (QD). Sorafenib was administered as 2*200-mg capsules in the AM and 2*200-mg capsules in the PM.

| | |
|-----------------------|----------|
| Reporting group title | Brivanib |
|-----------------------|----------|

Reporting group description:

Subjects received brivanib alaninate orally (800 mg QD) and sorafenib orally matched placebo BID. Brivanib alaninate was administered as 4*200-mg tablets and sorafenib matched placebo as 2*200-mg capsules in the AM and 2*200-mg capsules in the PM.

| Reporting group values | Sorafenib | Brivanib | Total |
|--|-----------------|---------------|-------|
| Number of subjects | 578 | 577 | 1155 |
| Age categorical Units: Subjects | | | |
| < 65 years | 371 | 343 | 714 |
| >= 65 years | 207 | 234 | 441 |
| Age continuous Units: years arithmetic mean standard deviation | 59.6 ± 12.06 | 60 ± 12.26 | - |
| Gender categorical Units: Subjects | | | |
| Female | 94 | 94 | 188 |
| Male | 484 | 483 | 967 |
| Performance Status Assessed by Eastern Cooperative Oncology Group (ECOG) | | | |
| Eastern Cooperative Oncology Group (ECOG) criteria is used to assess disease progression and affects on daily living abilities and to determine appropriate treatment and prognosis. Grade 0 = No restriction on activity, Grade 1 = Restricted physical activity but ambulatory and capable of light work | | | |
| Units: Subjects | | | |
| Grade 0 | 352 | 369 | 721 |
| Grade 1 | 226 | 208 | 434 |

End points

End points reporting groups

| | |
|---|-----------|
| Reporting group title | Sorafenib |
| Reporting group description: Subjects received sorafenib orally (400 mg BID) and brivanib alaninate orally matched placebo once daily (QD). Sorafenib was administered as 2*200-mg capsules in the AM and 2*200-mg capsules in the PM. | |
| Reporting group title | Brivanib |
| Reporting group description: Subjects received brivanib alaninate orally (800 mg QD) and sorafenib orally matched placebo BID. Brivanib alaninate was administered as 4*200-mg tablets and sorafenib matched placebo as 2*200-mg capsules in the AM and 2*200-mg capsules in the PM. | |
| Reporting group title | Sorafenib |
| Reporting group description: Subjects received sorafenib orally (400 mg BID) and brivanib alaninate orally matched placebo QD in the treatment period. No treatment was received in the follow-up. | |
| Reporting group title | Brivanib |
| Reporting group description: Subjects received brivanib alaninate orally (800 mg QD) and sorafenib orally matched placebo BID in the treatment period. No treatment was received in the follow-up. | |

Primary: Overall Survival (OS): Non-inferiority of brivanib versus sorafenib

| | |
|---|---|
| End point title | Overall Survival (OS): Non-inferiority of brivanib versus sorafenib |
| End point description: OS was computed for all per protocol subjects under non-inferiority test and was defined as time in months from the randomization date to the date of death due to any cause. If the subject did not die, survival was censored on the last date he or she was known to be alive. The analysis was performed in all the subjects in the per protocol population; all randomized subjects except for those who 1) had wrong diagnosis of cancer; 2) were not treated; 3) were not treated with the study therapy as assigned by the randomization. Non-inferiority of the brivanib-containing arms compared with the sorafenib-containing arms was investigated. | |
| End point type | Primary |
| End point timeframe: From randomization to death or date of last censoring (up to approximately 35 months) | |

| End point values | Sorafenib | Brivanib | | |
|----------------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 574 | 575 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 9.9 (8.5 to 11.5) | 9.5 (8.4 to 10.7) | | |

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Overall Survival: brivanib vs sorafenib |
| Statistical analysis description: | |
| Analysis compared survival in arms by stratified, 2-sided, alpha=0.05 level, log-rank test. Null hypothesis=survival was equal in both arms. | |
| Comparison groups | Sorafenib v Brivanib |
| Number of subjects included in analysis | 1149 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.373 ^[1] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.06 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.93 |
| upper limit | 1.22 |

Notes:

[1] - Stratified by ECOG Performance Status (0 vs 1), region (Asia vs Rest), extrahepatic spread and/or vascular invasion at randomization

Primary: Overall Survival (OS): Superiority of brivanib versus sorafenib

| | |
|---|---|
| End point title | Overall Survival (OS): Superiority of brivanib versus sorafenib |
| End point description: | |
| OS was computed for all randomized subjects under superiority test and was defined as time in months from the randomization date to the date of death due to any cause. If the subject did not die, survival was censored on the last date he or she was known to be alive. However, some subjects did not have a best overall response by investigators and were classified as unevaluable. The analysis was performed in all the subjects who were randomized to receive any study treatment. Superiority of the brivanib-containing arms compared with the sorafenib-containing arms was investigated. | |
| End point type | Primary |
| End point timeframe: | |
| From randomization to death or date of last censoring (up to approximately 35 months) | |

| End point values | Sorafenib | Brivanib | | |
|----------------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 578 | 577 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 9.9 (8.5 to 11.5) | 9.5 (8.3 to 10.6) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Overall Survival: brivanib vs sorafenib |
| Statistical analysis description: | |
| Analysis compared survival in arms by stratified, 2-sided, alpha=0.05 level, log-rank test. Null hypothesis=survival was equal in both arms. Power calculations indicated that >=817 deaths would lead to approximately 89% power at 5% level for rejecting null hypothesis, given a true hazard ratio of 0.80. | |
| Comparison groups | Brivanib v Sorafenib |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 1155 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3116 ^[2] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.07 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.94 |
| upper limit | 1.23 |

Notes:

[2] - Stratified by ECOG Performance Status (0 vs 1), region (Asia vs Rest), extrahepatic spread and/or vascular invasion at randomization

Secondary: Time to Progression (TTP)

| | |
|-----------------|---------------------------|
| End point title | Time to Progression (TTP) |
|-----------------|---------------------------|

End point description:

Time to progression was defined as the time from randomization to the time of radiographic disease progression. Subjects without progression were censored at their last tumor assessment date and those who had no on-study tumor assessment were censored at the date of randomization. TTP was based on tumor assessments made by the investigators according to the Modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria for HCC, based on RECIST (version 1.0). mRECIST introduced the concept of the longest diameter of the viable tumor tissue for "typical" intrahepatic HCC lesions, those that displayed hypervascularity in the arterial phase and a wash-out in the portal or late venous phase in dynamic contrast-enhanced spiral CT or MRI. The analysis was performed in all randomized subjects; subjects randomized to any treatment, however some subjects did not have a best overall response by investigators and were classified as unevaluable.

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

End point timeframe:

From randomization to time of radiographic disease progression (up to approximately 31 months)

| End point values | Sorafenib | Brivanib | | |
|----------------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 578 | 577 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 4.1 (3.1 to 4.2) | 4.2 (4.1 to 4.3) | | |

Statistical analyses

| | |
|----------------------------|-----------------------------|
| Statistical analysis title | TTP (brivanib vs sorafenib) |
|----------------------------|-----------------------------|

Statistical analysis description:

The primary comparison of TTP between treatment arms utilized a two-sided, $\alpha = 0.05$ level, stratified log-rank test (stratified by ECOG PS (0 vs 1), presence of extra-hepatic spread and/or vascular invasion (yes vs no) at the time of randomization and region (Asia vs Rest)).

| | |
|-------------------|----------------------|
| Comparison groups | Sorafenib v Brivanib |
|-------------------|----------------------|

| | |
|---|-------------------------|
| Number of subjects included in analysis | 1155 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8532 ^[3] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.88 |
| upper limit | 1.16 |

Notes:

[3] - Stratified by ECOG Performance Status (0 vs 1), region (Asia vs Rest), extrahepatic spread and/or vascular invasion at randomization

Secondary: Objective Response Rate (ORR) and Disease Control Rate (DCR)

| | |
|-----------------|--|
| End point title | Objective Response Rate (ORR) and Disease Control Rate (DCR) |
|-----------------|--|

End point description:

ORR was defined as the proportion of randomized subjects in each treatment group whose best response was complete response (CR) or partial response (PR). DCR was defined as the proportion of randomized subjects in each treatment group whose best response was CR, PR, or stable disease (SD). ORR and DCR were assessed by the investigator using mRECIST criteria for HCC. Confidence intervals were based on the Clopper and Pearson method. The analysis was performed in all randomized subjects; subjects randomized to any treatment, however some subjects did not have a best overall response by investigators and were classified as unevaluable.

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

End point timeframe:

From randomization to time of disease progression or death, whichever occurs first (up to approximately 35 months)

| End point values | Sorafenib | Brivanib | | |
|----------------------------------|----------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 578 | 577 | | |
| Units: proportion of subjects | | | | |
| number (confidence interval 95%) | | | | |
| ORR | 8.8 (6.64 to 11.44) | 1.45 (0.99 to 2.13) | | |
| DCR | 64.7 (60.66 to 68.6) | 65.5 (61.47 to 69.39) | | |

Statistical analyses

| | |
|----------------------------|-----------------------------|
| Statistical analysis title | DCR (brivanib vs sorafenib) |
|----------------------------|-----------------------------|

Statistical analysis description:

DCR compared treatment arms using a two-sided, = 0.05 level, Cochran-Mantel-Haenszel test with an associated odds ratio estimate and 95% confidence interval, stratified by ECOG Performance Status (0 vs 1), region (Asia vs Rest), extrahepatic spread and/or vascular invasion at randomization.

| | |
|-------------------|----------------------|
| Comparison groups | Sorafenib v Brivanib |
|-------------------|----------------------|

| | |
|---|-------------------------|
| Number of subjects included in analysis | 1155 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8739 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.02 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.8 |
| upper limit | 1.3 |

| | |
|-----------------------------------|-----------------------------|
| Statistical analysis title | ORR (brivanib vs sorafenib) |
|-----------------------------------|-----------------------------|

Statistical analysis description:

ORR compared treatment arms using a two-sided, = 0.05 level, Cochran-Mantel-Haenszel test with an associated odds ratio estimate and 95% confidence interval, stratified by ECOG Performance Status (0 vs 1), region (Asia vs Rest), extrahepatic spread and/or vascular invasion at randomization.

| | |
|---|-------------------------|
| Comparison groups | Sorafenib v Brivanib |
| Number of subjects included in analysis | 1155 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0569 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.45 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.99 |
| upper limit | 2.13 |

Secondary: Median Time for Duration of Response (DOR) and Time to Response (TTR)

| | |
|-----------------|---|
| End point title | Median Time for Duration of Response (DOR) and Time to Response (TTR) |
|-----------------|---|

End point description:

DOR was defined as the time from randomization to disease progression or death for randomized subjects whose best response was PR or CR. TTR was defined as the time from randomization to the time when response criteria was met for PR or CR, whichever occurred first. The DOR and TTR analysis was performed in all randomized subjects whose best response was CR or PR. Subjects who neither progressed nor died were censored on the date of their last tumor assessment.

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

End point timeframe:

From randomization to time of disease progression or death, whichever occurs first (up to approximately 35 months)

| End point values | Sorafenib | Brivanib | | |
|----------------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 51 | 69 | | |
| Units: months | | | | |
| median (confidence interval 95%) | | | | |
| DOR | 4.5 (2.8 to 7) | 4.5 (4.2 to 5.8) | | |
| TTR | 1.5 (1.4 to 2.8) | 2.7 (1.5 to 2.8) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Disease Control (DDC)

| | |
|-----------------|-----------------------------------|
| End point title | Duration of Disease Control (DDC) |
|-----------------|-----------------------------------|

End point description:

Duration of disease control was defined as the time from randomization to disease progression or death for randomized subjects whose best response was PR, CR, or SD. The analysis was performed in all randomized subjects whose best response was PR, CR, or SD. Subjects who neither progressed nor died were censored on the date of their last tumor assessment.

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

End point timeframe:

From randomization to time of disease progression or death, whichever occurs first (up to approximately 35 months)

| End point values | Sorafenib | Brivanib | | |
|----------------------------------|------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 374 | 378 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 4.2 (2.9 to 4.3) | 3.8 (3 to 4.2) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Death, Serious Adverse Event (SAE), Adverse Event (AE) Leading to Discontinuation, and Grade 3 or higher AEs

| | |
|-----------------|--|
| End point title | Number of Subjects with Death, Serious Adverse Event (SAE), Adverse Event (AE) Leading to Discontinuation, and Grade 3 or higher AEs |
|-----------------|--|

End point description:

AE=any new unfavorable symptom, sign, or disease or worsening of a preexisting condition that may not have a causal relationship with treatment. SAE=a medical event that at any dose results in death, persistent or significant disability/incapacity, or drug dependency/abuse; is life-threatening, an important medical event, or a congenital anomaly/birth defect; or requires or prolongs hospitalization. Grade (Gr) 1=Mild, Gr 2=Moderate, Gr 3=Severe, Gr 4= Potentially Life-threatening or disabling. Grading per the National Cancer Institute Common Terminology Criteria (NCI CTC) Version 3.0 criteria. The analysis was performed in all treated subjects; subjects who received at least one dose of study medications. BMS excluded 27 subjects (9 from Taiwan per the Taiwan Food and Drug Administration [TFDA] Health Authority request and 18 from India due to unreliable data) from both the overall safety and efficacy analyses.

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

End point timeframe:

Date of first dose of study drug to 30 days post last dose of study drug (up to approximately 35 months)

| End point values | Sorafenib | Brivanib | | |
|--------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 575 | 575 | | |
| Units: subjects | | | | |
| Death | 96 | 93 | | |
| SAEs | 299 | 339 | | |
| AEs Leading to Discontinuation | 192 | 246 | | |
| >= Grade 3 AEs | 463 | 473 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On Study (i.e. events from 1st dose date through last dose date + 30 days); up to approximately 35 months.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 15.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|----------|
| Reporting group title | Brivanib |
|-----------------------|----------|

Reporting group description:

In the treatment period, subjects received brivanib alaninate orally (800 mg QD) and sorafenib orally matched placebo BID. Brivanib alaninate was administered as 4*200mg tablets and sorafenib matched placebo as 2*200mg capsules in the AM and 2*200mg capsules in the PM. In the follow-up period, no treatment was received.

| | |
|-----------------------|-----------|
| Reporting group title | Sorafenib |
|-----------------------|-----------|

Reporting group description:

In the treatment period, subjects received sorafenib orally (400 mg BID) and brivanib alaninate orally matched placebo QD. Sorafenib was administered as 2*200mg capsules in the AM and 2*200mg capsules in the PM. In the follow-up period, no treatment was received.

| Serious adverse events | Brivanib | Sorafenib | |
|---|--------------------|--------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 339 / 575 (58.96%) | 299 / 575 (52.00%) | |
| number of deaths (all causes) | 93 | 96 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Bone cancer metastatic | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cancer pain | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colon neoplasm | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|--|------------------|-----------------|--|
| Hepatic cancer metastatic subjects affected / exposed | 1 / 575 (0.17%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hepatic neoplasm malignant subjects affected / exposed | 10 / 575 (1.74%) | 9 / 575 (1.57%) | |
| occurrences causally related to treatment / all | 0 / 10 | 0 / 9 | |
| deaths causally related to treatment / all | 0 / 7 | 0 / 6 | |
| Intracranial tumour haemorrhage subjects affected / exposed | 1 / 575 (0.17%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Liver carcinoma ruptured subjects affected / exposed | 1 / 575 (0.17%) | 3 / 575 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Lung neoplasm malignant subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung squamous cell carcinoma stage unspecified subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to central nervous system subjects affected / exposed | 1 / 575 (0.17%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Metastases to spine subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neoplasm malignant | | | |

| | | | |
|---|-------------------|--------------------|--|
| subjects affected / exposed | 92 / 575 (16.00%) | 114 / 575 (19.83%) | |
| occurrences causally related to treatment / all | 0 / 94 | 0 / 118 | |
| deaths causally related to treatment / all | 0 / 42 | 0 / 45 | |
| Squamous cell carcinoma of skin | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tonsil cancer | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Treatment related secondary malignancy | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tumour associated fever | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tumour flare | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tumour haemorrhage | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 3 / 575 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Tumour necrosis | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tumour pain | | | |

| | | | |
|---|------------------|-----------------|--|
| subjects affected / exposed | 1 / 575 (0.17%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tumour rupture | | | |
| subjects affected / exposed | 3 / 575 (0.52%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Vascular disorders | | | |
| Arterial stenosis | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Embolism | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertension | | | |
| subjects affected / exposed | 14 / 575 (2.43%) | 4 / 575 (0.70%) | |
| occurrences causally related to treatment / all | 15 / 16 | 3 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 3 / 575 (0.52%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |
| subjects affected / exposed | 3 / 575 (0.52%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral arterial occlusive disease | | | |

| | | | |
|--|------------------|------------------|--|
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Phlebitis | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 7 / 575 (1.22%) | 6 / 575 (1.04%) | |
| occurrences causally related to treatment / all | 6 / 8 | 4 / 6 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Chest pain | | | |
| subjects affected / exposed | 2 / 575 (0.35%) | 3 / 575 (0.52%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chills | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Death | | | |
| subjects affected / exposed | 2 / 575 (0.35%) | 6 / 575 (1.04%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 6 | |
| Fatigue | | | |
| subjects affected / exposed | 28 / 575 (4.87%) | 13 / 575 (2.26%) | |
| occurrences causally related to treatment / all | 28 / 31 | 6 / 14 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Gait disturbance | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical health deterioration | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 7 / 575 (1.22%) | 3 / 575 (0.52%) | |
| occurrences causally related to treatment / all | 5 / 7 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Generalised oedema | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malaise | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 2 / 575 (0.35%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multi-Organ failure | | | |
| subjects affected / exposed | 2 / 575 (0.35%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | |
| Oedema | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 3 / 575 (0.52%) | 3 / 575 (0.52%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 2 / 575 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Performance status decreased | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 1 / 575 (0.17%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 8 / 575 (1.39%) | 16 / 575 (2.78%) | |
| occurrences causally related to treatment / all | 2 / 8 | 4 / 18 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sudden death | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute pulmonary oedema | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 2 / 575 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Asthma | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 2 / 575 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cough | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 5 / 575 (0.87%) | 4 / 575 (0.70%) | |
| occurrences causally related to treatment / all | 2 / 5 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Epistaxis | | | |
| subjects affected / exposed | 4 / 575 (0.70%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Haemoptysis | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hiccups | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hydrothorax | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung disorder | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 5 / 575 (0.87%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumomediastinum | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonitis | | | |
| subjects affected / exposed | 2 / 575 (0.35%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumothorax | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Productive cough | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 3 / 575 (0.52%) | 3 / 575 (0.52%) | |
| occurrences causally related to treatment / all | 1 / 3 | 1 / 3 | |
| deaths causally related to treatment / all | 1 / 2 | 0 / 1 | |
| Respiratory distress | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Confusional state | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 575 (0.35%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Delirium | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Depression | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Disorientation | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Insomnia | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mental status changes | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mood altered | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Activated partial thromboplastin time prolonged | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Alanine aminotransferase increased | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 575 (0.17%) | 3 / 575 (0.52%) | |
| occurrences causally related to treatment / all | 1 / 1 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 7 / 575 (1.22%) | 4 / 575 (0.70%) | |
| occurrences causally related to treatment / all | 5 / 7 | 2 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 3 / 575 (0.52%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood chloride decreased | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood potassium decreased | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood sodium decreased | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ejection fraction abnormal | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical condition abnormal | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemoglobin decreased | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 4 / 575 (0.70%) | 2 / 575 (0.35%) | |
| occurrences causally related to treatment / all | 3 / 4 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| International normalised ratio increased | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lipase increased | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Liver function test abnormal | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutrophil count increased | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Platelet count decreased | | | |
| subjects affected / exposed | 2 / 575 (0.35%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Protein urine present | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transaminases increased | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Accidental overdose | | | |
| subjects affected / exposed | 4 / 575 (0.70%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acetabulum fracture | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Compression fracture | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Contusion | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 2 / 575 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fall | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Femoral neck fracture | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femur fracture | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fracture | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 575 (0.17%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Heat stroke | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic rupture | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Hip fracture | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Humerus fracture | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 2 / 575 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Overdose | | | |
| subjects affected / exposed | 11 / 575 (1.91%) | 12 / 575 (2.09%) | |
| occurrences causally related to treatment / all | 2 / 14 | 1 / 14 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pelvic fracture | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal fracture | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subdural haematoma | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 3 / 575 (0.52%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial flutter | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest | | | |
| subjects affected / exposed | 2 / 575 (0.35%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardio-Respiratory arrest | | | |
| subjects affected / exposed | 3 / 575 (0.52%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 3 | 0 / 0 | |
| Cardiogenic shock | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cardiopulmonary failure | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Supraventricular extrasystoles | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tachycardia | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular tachycardia | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Cerebellar haemorrhage | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 7 / 575 (1.22%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 4 / 7 | 0 / 1 | |
| deaths causally related to treatment / all | 1 / 3 | 0 / 1 | |
| Cerebral infarction | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Cerebral ischaemia | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 3 / 575 (0.52%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cognitive disorder | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coma hepatic | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Convulsion | | | |
| subjects affected / exposed | 2 / 575 (0.35%) | 2 / 575 (0.35%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Depressed level of consciousness | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dizziness | | | |
| subjects affected / exposed | 2 / 575 (0.35%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysarthria | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Encephalopathy | | | |
| subjects affected / exposed | 8 / 575 (1.39%) | 3 / 575 (0.52%) | |
| occurrences causally related to treatment / all | 3 / 9 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epiduritis | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epilepsy | | | |
| subjects affected / exposed | 2 / 575 (0.35%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhagic stroke | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Headache | | | |
| subjects affected / exposed | 3 / 575 (0.52%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hemiparesis | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic encephalopathy | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 20 / 575 (3.48%) | 10 / 575 (1.74%) | |
| occurrences causally related to treatment / all | 12 / 26 | 2 / 12 | |
| deaths causally related to treatment / all | 0 / 4 | 0 / 3 | |
| Hypoglycaemic coma | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemic stroke | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Loss of consciousness | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Memory impairment | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Monoplegia | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Paralysis | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral sensory neuropathy | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Posterior reversible encephalopathy syndrome | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Presyncope | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sensory disturbance | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Somnolence | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Speech disorder | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombotic stroke | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tremor | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 575 (0.35%) | 4 / 575 (0.70%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukocytosis | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 5 / 575 (0.87%) | 4 / 575 (0.70%) | |
| occurrences causally related to treatment / all | 5 / 5 | 2 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombotic microangiopathy | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Diplopia | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vision blurred | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 5 / 575 (0.87%) | 2 / 575 (0.35%) | |
| occurrences causally related to treatment / all | 1 / 5 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain | | | |
| subjects affected / exposed | 19 / 575 (3.30%) | 16 / 575 (2.78%) | |
| occurrences causally related to treatment / all | 3 / 21 | 1 / 18 | |
| deaths causally related to treatment / all | 1 / 2 | 0 / 1 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 8 / 575 (1.39%) | 6 / 575 (1.04%) | |
| occurrences causally related to treatment / all | 2 / 8 | 0 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anal haemorrhage | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anal ulcer | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ascites | | | |
| subjects affected / exposed | 14 / 575 (2.43%) | 16 / 575 (2.78%) | |
| occurrences causally related to treatment / all | 5 / 16 | 2 / 16 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 4 / 575 (0.70%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 4 / 5 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dental caries | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diaphragmatic hernia | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 18 / 575 (3.13%) | 13 / 575 (2.26%) | |
| occurrences causally related to treatment / all | 15 / 21 | 10 / 14 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Duodenal ulcer | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enteritis | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric haemorrhage | | | |
| subjects affected / exposed | 2 / 575 (0.35%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric ulcer | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 2 / 575 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric ulcer haemorrhage | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 575 (0.17%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric varices haemorrhage | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorder | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 6 / 575 (1.04%) | 7 / 575 (1.22%) | |
| occurrences causally related to treatment / all | 3 / 7 | 3 / 7 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | |
| Gastrointestinal motility disorder | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematemesis | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Haematochezia | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus | | | |

| | | | |
|---|------------------|-----------------|--|
| subjects affected / exposed | 0 / 575 (0.00%) | 3 / 575 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Inguinal hernia | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 2 / 575 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 2 / 575 (0.35%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intra-Abdominal haemorrhage | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Melaena | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 9 / 575 (1.57%) | 2 / 575 (0.35%) | |
| occurrences causally related to treatment / all | 7 / 9 | 0 / 2 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Oesophageal varices haemorrhage | | | |
| subjects affected / exposed | 10 / 575 (1.74%) | 9 / 575 (1.57%) | |
| occurrences causally related to treatment / all | 3 / 11 | 2 / 9 | |
| deaths causally related to treatment / all | 0 / 2 | 1 / 1 | |
| Pancreatitis | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis acute | | | |

| | | | |
|---|------------------|-----------------|--|
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Periodontitis | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal perforation | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stomatitis | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 4 / 575 (0.70%) | 8 / 575 (1.39%) | |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 8 | |
| deaths causally related to treatment / all | 1 / 2 | 0 / 3 | |
| Vomiting | | | |
| subjects affected / exposed | 12 / 575 (2.09%) | 2 / 575 (0.35%) | |
| occurrences causally related to treatment / all | 10 / 14 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hepatobiliary disorders | | | |
| Acute hepatic failure | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bile duct stenosis | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (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 | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholangitis acute | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 2 / 575 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholestasis | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dilatation intrahepatic duct acquired | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gallbladder obstruction | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemobilia | | | |
| subjects affected / exposed | 2 / 575 (0.35%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic cirrhosis | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 2 / 575 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Hepatic failure | | | |
| subjects affected / exposed | 13 / 575 (2.26%) | 12 / 575 (2.09%) | |
| occurrences causally related to treatment / all | 3 / 13 | 1 / 14 | |
| deaths causally related to treatment / all | 1 / 6 | 0 / 7 | |
| Hepatic function abnormal | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 6 / 575 (1.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 3 | |
| Hepatic haemorrhage | | | |
| subjects affected / exposed | 2 / 575 (0.35%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatorenal syndrome | | | |
| subjects affected / exposed | 2 / 575 (0.35%) | 3 / 575 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 2 | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 13 / 575 (2.26%) | 12 / 575 (2.09%) | |
| occurrences causally related to treatment / all | 6 / 17 | 4 / 15 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Jaundice | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Jaundice cholestatic | | | |
| subjects affected / exposed | 2 / 575 (0.35%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Portal vein thrombosis | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Diabetic foot | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Erythema multiforme | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperhidrosis | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Palmar-Plantar erythrodysaesthesia syndrome | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 2 / 575 (0.35%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rash | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 3 / 575 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin necrosis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 575 (0.00%) | 2 / 575 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stevens-Johnson syndrome | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Calculus bladder | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nephrotic syndrome | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Proteinuria | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure | | | |
| subjects affected / exposed | 5 / 575 (0.87%) | 3 / 575 (0.52%) | |
| occurrences causally related to treatment / all | 2 / 7 | 1 / 3 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 1 | |
| Renal failure acute | | | |
| subjects affected / exposed | 3 / 575 (0.52%) | 5 / 575 (0.87%) | |
| occurrences causally related to treatment / all | 3 / 5 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |

| | | | |
|---|-----------------|-----------------|--|
| Hypothyroidism | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Inappropriate antidiuretic hormone secretion | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| 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 | 2 / 575 (0.35%) | 3 / 575 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bone pain | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 2 / 575 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Flank pain | | | |
| subjects affected / exposed | 2 / 575 (0.35%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Groin pain | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemarthrosis | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Muscular weakness | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 2 / 575 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 2 / 575 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteitis | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteoporotic fracture | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pathological fracture | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Anal abscess | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Biliary tract infection | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchopneumonia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea infectious | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 3 / 575 (0.52%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes zoster | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infected skin ulcer | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infection | | | |
| subjects affected / exposed | 3 / 575 (0.52%) | 3 / 575 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Liver abscess | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 2 / 575 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 3 / 575 (0.52%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung infection | | | |
| subjects affected / exposed | 2 / 575 (0.35%) | 2 / 575 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Neutropenic infection | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| 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 | 2 / 575 (0.35%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 7 / 575 (1.22%) | 4 / 575 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 4 | |
| deaths causally related to treatment / all | 1 / 3 | 0 / 1 | |
| Postoperative wound infection | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 2 / 575 (0.35%) | 3 / 575 (0.52%) | |
| occurrences causally related to treatment / all | 0 / 3 | 3 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Septic shock | | | |

| | | | |
|---|------------------|-----------------|--|
| subjects affected / exposed | 1 / 575 (0.17%) | 2 / 575 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Tuberculous pleurisy | | | |
| subjects affected / exposed | 1 / 575 (0.17%) | 0 / 575 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 2 / 575 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 7 / 575 (1.22%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 8 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound infection | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 20 / 575 (3.48%) | 6 / 575 (1.04%) | |
| occurrences causally related to treatment / all | 15 / 20 | 4 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dehydration | | | |
| subjects affected / exposed | 14 / 575 (2.43%) | 3 / 575 (0.52%) | |
| occurrences causally related to treatment / all | 8 / 15 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 2 / 575 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hyperglycaemia | | | |

| | | | |
|---|------------------|-----------------|--|
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 9 / 575 (1.57%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 3 / 9 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 2 / 575 (0.35%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 2 / 575 (0.35%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 30 / 575 (5.22%) | 6 / 575 (1.04%) | |
| occurrences causally related to treatment / all | 26 / 34 | 5 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Tumour lysis syndrome | | | |
| subjects affected / exposed | 0 / 575 (0.00%) | 1 / 575 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Brivanib | Sorafenib | |
|---|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 553 / 575 (96.17%) | 558 / 575 (97.04%) | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 235 / 575 (40.87%) | 153 / 575 (26.61%) | |
| occurrences (all) | 276 | 178 | |
| General disorders and administration site conditions | | | |

| | | | |
|---|--------------------|--------------------|--|
| Asthenia | | | |
| subjects affected / exposed | 62 / 575 (10.78%) | 43 / 575 (7.48%) | |
| occurrences (all) | 80 | 50 | |
| Chest pain | | | |
| subjects affected / exposed | 25 / 575 (4.35%) | 33 / 575 (5.74%) | |
| occurrences (all) | 46 | 38 | |
| Fatigue | | | |
| subjects affected / exposed | 293 / 575 (50.96%) | 194 / 575 (33.74%) | |
| occurrences (all) | 372 | 244 | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 33 / 575 (5.74%) | 24 / 575 (4.17%) | |
| occurrences (all) | 41 | 26 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 81 / 575 (14.09%) | 64 / 575 (11.13%) | |
| occurrences (all) | 105 | 71 | |
| Pain | | | |
| subjects affected / exposed | 26 / 575 (4.52%) | 32 / 575 (5.57%) | |
| occurrences (all) | 37 | 37 | |
| Pyrexia | | | |
| subjects affected / exposed | 85 / 575 (14.78%) | 114 / 575 (19.83%) | |
| occurrences (all) | 129 | 150 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 79 / 575 (13.74%) | 78 / 575 (13.57%) | |
| occurrences (all) | 96 | 96 | |
| Dysphonia | | | |
| subjects affected / exposed | 102 / 575 (17.74%) | 60 / 575 (10.43%) | |
| occurrences (all) | 119 | 67 | |
| Dyspnoea | | | |
| subjects affected / exposed | 47 / 575 (8.17%) | 50 / 575 (8.70%) | |
| occurrences (all) | 54 | 58 | |
| Epistaxis | | | |
| subjects affected / exposed | 31 / 575 (5.39%) | 27 / 575 (4.70%) | |
| occurrences (all) | 41 | 34 | |
| Oropharyngeal pain | | | |

| | | | |
|--|---|---|--|
| subjects affected / exposed occurrences (all) | 26 / 575 (4.52%) 30 | 32 / 575 (5.57%) 38 | |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 62 / 575 (10.78%) 70 | 50 / 575 (8.70%) 59 | |
| Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) Aspartate aminotransferase increased subjects affected / exposed occurrences (all) Blood alkaline phosphatase increased subjects affected / exposed occurrences (all) Blood bilirubin increased subjects affected / exposed occurrences (all) Haemoglobin decreased subjects affected / exposed occurrences (all) Lipase increased subjects affected / exposed occurrences (all) Platelet count decreased subjects affected / exposed occurrences (all) Weight decreased subjects affected / exposed occurrences (all) | 114 / 575 (19.83%) 144 145 / 575 (25.22%) 194 35 / 575 (6.09%) 38 39 / 575 (6.78%) 47 12 / 575 (2.09%) 15 12 / 575 (2.09%) 18 54 / 575 (9.39%) 74 121 / 575 (21.04%) 140 | 106 / 575 (18.43%) 127 157 / 575 (27.30%) 198 30 / 575 (5.22%) 32 41 / 575 (7.13%) 57 29 / 575 (5.04%) 42 38 / 575 (6.61%) 47 47 / 575 (8.17%) 76 119 / 575 (20.70%) 136 | |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache | 98 / 575 (17.04%) 123 | 42 / 575 (7.30%) 49 | |

| | | | |
|--|---------------------------|-------------------------|--|
| subjects affected / exposed occurrences (all) | 109 / 575 (18.96%) 150 | 62 / 575 (10.78%) 80 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 29 / 575 (5.04%) | 29 / 575 (5.04%) | |
| occurrences (all) | 33 | 37 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 52 / 575 (9.04%) | 48 / 575 (8.35%) | |
| occurrences (all) | 70 | 82 | |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 63 / 575 (10.96%) | 50 / 575 (8.70%) | |
| occurrences (all) | 65 | 54 | |
| Abdominal pain | | | |
| subjects affected / exposed | 178 / 575 (30.96%) | 181 / 575 (31.48%) | |
| occurrences (all) | 241 | 277 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 78 / 575 (13.57%) | 60 / 575 (10.43%) | |
| occurrences (all) | 90 | 73 | |
| Ascites | | | |
| subjects affected / exposed | 82 / 575 (14.26%) | 85 / 575 (14.78%) | |
| occurrences (all) | 89 | 90 | |
| Constipation | | | |
| subjects affected / exposed | 102 / 575 (17.74%) | 98 / 575 (17.04%) | |
| occurrences (all) | 129 | 116 | |
| Diarrhoea | | | |
| subjects affected / exposed | 275 / 575 (47.83%) | 284 / 575 (49.39%) | |
| occurrences (all) | 564 | 601 | |
| Dyspepsia | | | |
| subjects affected / exposed | 30 / 575 (5.22%) | 30 / 575 (5.22%) | |
| occurrences (all) | 36 | 37 | |
| Nausea | | | |
| subjects affected / exposed | 217 / 575 (37.74%) | 114 / 575 (19.83%) | |
| occurrences (all) | 306 | 139 | |
| Stomatitis | | | |

| | | | |
|---|---------------------------|---------------------------|--|
| subjects affected / exposed occurrences (all) | 37 / 575 (6.43%) 41 | 33 / 575 (5.74%) 38 | |
| Vomiting subjects affected / exposed occurrences (all) | 153 / 575 (26.61%) 248 | 95 / 575 (16.52%) 141 | |
| Hepatobiliary disorders Hyperbilirubinaemia subjects affected / exposed occurrences (all) | 110 / 575 (19.13%) 144 | 101 / 575 (17.57%) 126 | |
| Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all) | 12 / 575 (2.09%) 12 | 129 / 575 (22.43%) 134 | |
| Palmar-Plantar erythrodysesthesia syndrome subjects affected / exposed occurrences (all) | 103 / 575 (17.91%) 132 | 297 / 575 (51.65%) 353 | |
| Pruritus subjects affected / exposed occurrences (all) | 55 / 575 (9.57%) 61 | 72 / 575 (12.52%) 84 | |
| Rash subjects affected / exposed occurrences (all) | 57 / 575 (9.91%) 65 | 118 / 575 (20.52%) 136 | |
| Renal and urinary disorders Proteinuria subjects affected / exposed occurrences (all) | 70 / 575 (12.17%) 96 | 43 / 575 (7.48%) 51 | |
| Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all) | 77 / 575 (13.39%) 79 | 20 / 575 (3.48%) 20 | |
| Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) | 56 / 575 (9.74%) 64 | 57 / 575 (9.91%) 69 | |
| Muscular weakness | | | |

| | | | |
|------------------------------------|--------------------|--------------------|--|
| subjects affected / exposed | 32 / 575 (5.57%) | 21 / 575 (3.65%) | |
| occurrences (all) | 40 | 21 | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 43 / 575 (7.48%) | 42 / 575 (7.30%) | |
| occurrences (all) | 53 | 44 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 297 / 575 (51.65%) | 201 / 575 (34.96%) | |
| occurrences (all) | 390 | 236 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 31 / 575 (5.39%) | 15 / 575 (2.61%) | |
| occurrences (all) | 45 | 18 | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 63 / 575 (10.96%) | 51 / 575 (8.87%) | |
| occurrences (all) | 78 | 72 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 25 / 575 (4.35%) | 38 / 575 (6.61%) | |
| occurrences (all) | 31 | 48 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 137 / 575 (23.83%) | 67 / 575 (11.65%) | |
| occurrences (all) | 222 | 86 | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 3 / 575 (0.52%) | 43 / 575 (7.48%) | |
| occurrences (all) | 3 | 69 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|---|
| 21 October 2009 | Clarified the novel mRECIST response criteria for HCC wording in the protocol. Additionally, the following changes were incorporated: 1) clarification of inclusion and exclusion criteria, 2) update on safety and efficacy data of brivanib in HCC study, 3) update on drug-drug- and CYP450 interactions based on new study results, 4) clarification of the study time-and event-flowchart, 5) clarification of dose modification instructions, and 6) addition of instructions on the single nucleotide polymorphism (SNP) blood sampling. |
| 15 October 2010 | Incorporated the following major update: up to a maximum of 150 additional subjects were to be randomized into the study, increasing the total sample size from n = 1050 subjects to a maximum of n = 1200 subjects. |

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.

BMS excluded 27 subjects (9 from Taiwan per the Taiwan Food and Drug Administration [TFDA] Health Authority request and 18 from India due to unreliable data) from both the overall safety and efficacy analyses.

Notes: