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 (EMEA) 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	59.6	60	
standard deviation	± 12.06	± 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 unevauable.

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, = 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 Subects with Death, Serious Adverse Event (SAE), Adverse Event (AE) Leading to Discontinuation, and Grade 3 or higher AEs

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

subjects affected / exposed	109 / 575 (18.96%)	62 / 575 (10.78%)	
occurrences (all)	150	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	37 / 575 (6.43%)	33 / 575 (5.74%)	
occurrences (all)	41	38	
Vomiting			
subjects affected / exposed	153 / 575 (26.61%)	95 / 575 (16.52%)	
occurrences (all)	248	141	
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	110 / 575 (19.13%)	101 / 575 (17.57%)	
occurrences (all)	144	126	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	12 / 575 (2.09%)	129 / 575 (22.43%)	
occurrences (all)	12	134	
Palmar-Plantar erythrodysaesthesia syndrome			
subjects affected / exposed	103 / 575 (17.91%)	297 / 575 (51.65%)	
occurrences (all)	132	353	
Pruritus			
subjects affected / exposed	55 / 575 (9.57%)	72 / 575 (12.52%)	
occurrences (all)	61	84	
Rash			
subjects affected / exposed	57 / 575 (9.91%)	118 / 575 (20.52%)	
occurrences (all)	65	136	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	70 / 575 (12.17%)	43 / 575 (7.48%)	
occurrences (all)	96	51	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	77 / 575 (13.39%)	20 / 575 (3.48%)	
occurrences (all)	79	20	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	56 / 575 (9.74%)	57 / 575 (9.91%)	
occurrences (all)	64	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 CYPP450 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: