Clinical trial results:
A Randomized, Double-blind, Multi-center Phase III Study of Brivanib plus Best Supportive Care (BSC) Versus Placebo plus BSC in Subjects with Advanced Hepatocellular Carcinoma (HCC) Who Have Failed or Are Intolerant to Sorafenib: the BRISK Study

Summary

EudraCT number	2008-005084-34
Trial protocol	DE ES SE FR GR BE IT
Global end of trial date	15 November 2011

Results information

Result version number	v1 (current)
This version publication date	23 September 2018
First version publication date	23 September 2018

Trial information

Trial identification

Sponsor protocol code	CA182-034

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussée de la Hulpe 185, Brussels, Belgium, 1170
Public contact	Bristol-Myers Squibb International Corporation, EU Study Start-Up Unit, clinical.trials@bms.com
Scientific contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, 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	23 August 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 November 2011
Global end of trial reached?	Yes
Global end of trial date	15 November 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the overall survival (OS) of subjects with advanced HCC, who have progressed on/after or are intolerant to sorafenib, and receive brivanib alaninate plus BSC to those receiving placebo plus BSC.

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: -

Actual start date of recruitment	19 February 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 3
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Brazil: 17
Country: Number of subjects enrolled	Canada: 19
Country: Number of subjects enrolled	China: 16
Country: Number of subjects enrolled	France: 141
Country: Number of subjects enrolled	Germany: 25
Country: Number of subjects enrolled	Greece: 3
Country: Number of subjects enrolled	Hong Kong: 2
Country: Number of subjects enrolled	India: 6
Country: Number of subjects enrolled	Italy: 33
Country: Number of subjects enrolled	Japan: 60
Country: Number of subjects enrolled	Korea, Republic of: 101
Country: Number of subjects enrolled	Mexico: 9
Country: Number of subjects enrolled	Puerto Rico: 1
Country: Number of subjects enrolled	Russian Federation: 12
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	Taiwan: 39
Country: Number of subjects enrolled	United States: 72

Worldwide total number of subjects	565
EEA total number of subjects	208

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)	311
From 65 to 84 years	251
85 years and over	3

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

565 participants enrolled; 395 participants randomized; 170 were not randomized: 144 no longer met study criteria; 17 with drew consent; 1 adverse event; 1 poor/non-compliance; 1 died; 6 other

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Brivanib

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Brivanib Alaninate BMS-582664
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Brivanib alaninate (800 mg once daily [QD]), as 200-mg film-coated tablets administered orally

Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo Brivanib Alaninate BMS-582664
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo for Brivanib alaninate (800 mg once daily [QD]), as 200-mg film-coated tablets administered orally

Number of subjects in period 1[1]	Brivanib	Placebo
Started	263	132
Completed	26	11
Not completed	237	121
No Longer Meets Study Criteria	2	1
Subject Withdrew Consent	2	1

Adverse Event Unrelated to Study Drug	21	10
Poor/Non-compliance	-	2
Study Drug Toxicity	61	9
Request to Discontinue Study Treatment	19	5
Disease Progression	132	93

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 to be in the baseline period are not the same as the worldwide number enrolled in the trial as out of 565 subjects who were enrolled only 395 were randomised. 170 were not randomized.

Baseline characteristics

Reporting groups	
Reporting group title	Brivanib
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Brivanib	Placebo	Total
Number of subjects	263	132	395
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	139	76	215
From 65-84 years	122	55	177
85 years and over	2	1	3
Age continuous Units: years			
arithmetic mean	62.5	61.1	
standard deviation	± 12.14	± 12.86	-
Gender categorical Units: Subjects			
Female	47	19	66
Male	216	113	329

End points

End points reporting groups

Reporting group title	Brivanib
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: To compare overall survival of subjects with advanced HCC who have progressed on/after or are intolerant to Sorafenib and receive Brivanib plus best supportive care (BSC) to those receiving placebo plus BSC

End point title	To compare overall survival of subjects with advanced HCC who have progressed on/after or are intolerant to Sorafenib and receive Brivanib plus best supportive care (BSC) to those receiving placebo plus BSC

End point description:

Overall survival was defined per subject as the time from randomization to the time of death from any cause. The primary efficacy objective was to compare the OS of subjects with locally advanced or metastatic HCC (who have progressed on/after or are intolerant to sorafenib) who received brivanib alaninate plus BSC to those receiving placebo plus BSC.

End point type	Primary

End point timeframe:

computerized tomography (CT)/ magnetic resonance imaging (MRI) every six weeks until progression or death

End point values	Brivanib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	263	132		
Units: months				
median (confidence interval 95%)	9.4 (8.0 to 11.0)	8.2 (6.2 to 10.3)		

Statistical analyses

Statistical analysis title	Hazard Ratio (95.8%) Stratified Log-Rank

Statistical analysis description:

Stratified by ECOG PS(0 versus 1&2), whether subjects had progressed or were intolerant to sorafenib, extrahepatic spread and/or vascular invasion at randomization Confidence interval (CI) for the hazard

Comparison groups	Brivanib v Placebo
Number of subjects included in analysis	395
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3307 [1]
Method	STRATIFIED LOG-RANK P-VALUE
Parameter estimate	Hazard ratio (HR)
Point estimate	0.89

Confidence interval	
level	95.8 %
sides	2-sided
lower limit	0.69
upper limit	1.15

Notes:

[1] - No statistical claim can be made because of hierarchical testing

Secondary: To compare time to progression (TTP) (Investigator assessed using modified Response Evaluation Criteria In Solid Tumors (RECIST) for HCC criteria)

End point title	To compare time to progression (TTP) (Investigator assessed using modified Response Evaluation Criteria In Solid Tumors (RECIST) for HCC criteria)

End point description:

Time to progression was defined as the time (in months) from randomization to the time of radiographic disease progression. Time to Progression as Assessed by the IRRC Using HCC mRECIST Criteria (Censoring for Additional Follow-up Anticancer Therapy)

End point type	Secondary

End point timeframe:

35 months

End point values	Brivanib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	263	132		
Units: months				
median (confidence interval 95%)	4.2 (3.0 to 4.5)	2.7 (1.5 to 2.8)		

Statistical analyses

Statistical analysis title	STRATIFIED LOG-RANK P-VALUE

Statistical analysis description:

Stratified by ECOG PS(0 versus 1&2), whether subjects had progressed or were intolerant to sorafenib, extrahepatic spread and/or vascular invasion at randomization

Comparison groups	Brivanib v Placebo
Number of subjects included in analysis	395
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	Stratified Log-Rank P-Value
Parameter estimate	Hazard ratio (HR)
Point estimate	0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	0.76

Secondary: To compare the Independent Radiological Review Committee (IRRC) assessed disease control rate (DCR) using modified RECIST for HCC criteria

End point title	To compare the Independent Radiological Review Committee (IRRC) assessed disease control rate (DCR) using modified RECIST for HCC criteria

End point description:

Disease control rate was defined as the number of CR, PR or stable disease (SD) divided by the total number of response-evaluable subjects as assessed by IRRC using mRECIST criteria for HCC.

End point type	Secondary

End point timeframe:

35 months

End point values	Brivanib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	263	132		
Units: number of subject				
arithmetic mean (confidence interval 95%)	71.2 (64.86 to 77.05)	49.1 (39.33 to 58.87)		

Statistical analyses

Statistical analysis title	COCHRAN-MANTEL-HAENSZEL

Statistical analysis description:

Stratified by ECOG PS(0 versus 1&2), whether subjects had progressed or were intolerant to sorafenib, extrahepatic spread and/or vascular invasion at randomization

Comparison groups	Brivanib v Placebo
Number of subjects included in analysis	395
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	2.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.65
upper limit	4.38

Secondary: To compare the Independent Radiological Review Committee (IRCC) assessed Objective Response Rate (ORR) using modified RECIST for HCC criteria

End point title	To compare the Independent Radiological Review Committee

	(IRCC) assessed Objective Response Rate (ORR) using modified RECIST for HCC criteria

End point description:

Objective response rate was defined as the number of responders (complete response [CR] and partial response [PR]) divided by the total number of response-evaluable subjects as assessed by IRRC using mRECIST criteria for HCC.

End point type	Secondary

End point timeframe:

35 months

End point values	Brivanib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	263	132		
Units: Number of Subjects (percentage)				
arithmetic mean (confidence interval 95%)	11.5 (7.65 to 16.40)	1.9 (0.23 to 6.53)		

Statistical analyses

Statistical analysis title	COCHRAN-MANTEL-HAENSZEL

Statistical analysis description:

Stratified by ECOG PS(0 versus 1&2), whether subjects had progressed or were intolerant to sorafenib, extra-hepatic spread and/or vascular invasion at randomization

Comparison groups	Brivanib v Placebo
Number of subjects included in analysis	395
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0032 [2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	5.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.4
upper limit	23.62

Notes:

[2] - No statistical claim can be made because of hierarchical testing

Secondary: To assess time to response (TTR)

End point title	To assess time to response (TTR)

End point description:

Secondary endpoint were based on independent radiology review committee (IRRC)-assessed progression and tumor response using modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria for HCC.

End point type	Secondary

End point timeframe:

6 weeks

End point values	Brivanib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	2		
Units: months				
median (confidence interval 95%)	1.4 (1.4 to 2.7)	2.2 (1.7 to 2.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: To assess duration of response (DOR)

End point title	To assess duration of response (DOR)

End point description:

Secondary endpoint were based on independent radiology review committee (IRRC)-assessed progression and tumor response using modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria for HCC.

End point type	Secondary

End point timeframe:

6 weeks

End point values	Brivanib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	2		
Units: months				
median (confidence interval 95%)	5.6 (4.2 to 9.5)	6.6 (5.6 to 7.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: To assess duration of disease control (DDC)

End point title	To assess duration of disease control (DDC)

End point description:

Secondary endpoint were based on independent radiology review committee (IRRC)-assessed progression and tumor response using modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria for HCC.

End point type	Secondary

End point timeframe:

6 weeks

End point values	Brivanib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	161	53		
Units: months				
median (confidence interval 95%)	2.7 (1.5 to 4.2)	3.4 (2.9 to 4.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: To assess safety profile of brivanib. Safety will be assessed by the number of adverse events (AEs), serious adverse events (SAEs), periodic data monitoring committee (DMC) review

End point title	To assess safety profile of brivanib. Safety will be assessed by the number of adverse events (AEs), serious adverse events (SAEs), periodic data monitoring committee (DMC) review

End point description:

Includes AE with onset on or after the first dosing date and on or prior to the last dosing date +14 days. Includes SAE with onset on or after the first dosing date and on or prior to the last dosing date +30 days. Related AE or SAE defined as AE or SAE with Related or Missing relationship to study medication MedDRA Version: 14.1

End point type	Secondary

End point timeframe:

35 months

End point values	Brivanib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	261	131		
Units: number of subjects				
number (not applicable)				
Adverse Events	259	123		
Serious Adverse Events	165	74		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On-treatment Adverse events (AEs) and serious AEs (SAE) were reported with onset on or after the first dosing date and on or prior to the last dosing date +14 days and +30 days respectively.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups

Reporting group title	Brivanib

Reporting group description:

Brivanib 800 mg oral tablet dosed once daily until disease progression or toxicity.

Reporting group title	Placebo

Reporting group description:

Placebo 0 mg oral tablet dosed once daily until disease progression or toxicity.

Serious adverse events	Brivanib	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	165 / 261 (63.22%)	74 / 131 (56.49%)	
number of deaths (all causes)	182	100	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Brain cancer metastatic			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cancer pain			
subjects affected / exposed	1 / 261 (0.38%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic neoplasm malignant			
subjects affected / exposed	2 / 261 (0.77%)	3 / 131 (2.29%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial tumour haemorrhage			

subjects affected / exposed	0 / 261 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver carcinoma ruptured			
subjects affected / exposed	1 / 261 (0.38%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastases to central nervous system			
subjects affected / exposed	1 / 261 (0.38%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple myeloma			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm malignant			
subjects affected / exposed	45 / 261 (17.24%)	27 / 131 (20.61%)	
occurrences causally related to treatment / all	0 / 46	0 / 28	
deaths causally related to treatment / all	0 / 16	0 / 14	
Neoplasm progression			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tongue neoplasm malignant stage unspecified			
subjects affected / exposed	0 / 261 (0.00%)	1 / 131 (0.76%)	
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 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	0 / 261 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aneurysm ruptured			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	2 / 261 (0.77%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	2 / 261 (0.77%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	2 / 261 (0.77%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	3 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Fatigue			
subjects affected / exposed	7 / 261 (2.68%)	2 / 131 (1.53%)	
occurrences causally related to treatment / all	7 / 8	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	7 / 261 (2.68%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	5 / 8	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Malaise			
subjects affected / exposed	2 / 261 (0.77%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema			
subjects affected / exposed	1 / 261 (0.38%)	2 / 131 (1.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	3 / 261 (1.15%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	2 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	6 / 261 (2.30%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	1 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Immune system disorders			
Liver and pancreas transplant rejection			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Reproductive system and breast disorders			
Epididymal cyst			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Bronchitis chronic			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (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	3 / 261 (1.15%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 261 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 261 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infiltration			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			

subjects affected / exposed	3 / 261 (1.15%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	3 / 261 (1.15%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	2 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 261 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 261 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delusion			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disorientation			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug abuse			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 261 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase			

increased			
subjects affected / exposed	3 / 261 (1.15%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	1 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-Reactive protein increased			
subjects affected / exposed	2 / 261 (0.77%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical condition abnormal			
subjects affected / exposed	0 / 261 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Weight decreased			
subjects affected / exposed	0 / 261 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 261 (0.00%)	2 / 131 (1.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Overdose			
subjects affected / exposed	2 / 261 (0.77%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	0 / 261 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 261 (0.38%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure congestive			
subjects affected / exposed	0 / 261 (0.00%)	1 / 131 (0.76%)	
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	0 / 261 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ventricular fibrillation			

subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Brain oedema			
subjects affected / exposed	2 / 261 (0.77%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (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 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coma			
subjects affected / exposed	2 / 261 (0.77%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coma hepatic			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dizziness			
subjects affected / exposed	2 / 261 (0.77%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Encephalopathy			

subjects affected / exposed	3 / 261 (1.15%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			
subjects affected / exposed	12 / 261 (4.60%)	2 / 131 (1.53%)	
occurrences causally related to treatment / all	7 / 12	1 / 2	
deaths causally related to treatment / all	2 / 4	0 / 1	
Metabolic encephalopathy			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Neuralgia			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraplegia			
subjects affected / exposed	0 / 261 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	2 / 261 (0.77%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	0 / 261 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			

subjects affected / exposed	1 / 261 (0.38%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic encephalopathy			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (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 / 261 (0.77%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neutropenia			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 261 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	0 / 261 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal artery occlusion			
subjects affected / exposed	0 / 261 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal artery thrombosis			

subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (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	2 / 261 (0.77%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	9 / 261 (3.45%)	9 / 131 (6.87%)	
occurrences causally related to treatment / all	5 / 12	1 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	2 / 261 (0.77%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	7 / 261 (2.68%)	5 / 131 (3.82%)	
occurrences causally related to treatment / all	7 / 8	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 261 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	5 / 261 (1.92%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	1 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			

subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric varices haemorrhage			
subjects affected / exposed	0 / 261 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 261 (0.77%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haematemesis			
subjects affected / exposed	2 / 261 (0.77%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal haemorrhage			
subjects affected / exposed	0 / 261 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Melaena			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	3 / 261 (1.15%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal haemorrhage			
subjects affected / exposed	0 / 261 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal varices haemorrhage			

subjects affected / exposed	4 / 261 (1.53%)	2 / 131 (1.53%)	
occurrences causally related to treatment / all	1 / 6	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 1	
Periodontitis			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	3 / 261 (1.15%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varices oesophageal			
subjects affected / exposed	1 / 261 (0.38%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	4 / 261 (1.53%)	2 / 131 (1.53%)	
occurrences causally related to treatment / all	4 / 4	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	1 / 261 (0.38%)	2 / 131 (1.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Bile duct obstruction			

subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 261 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	8 / 261 (3.07%)	2 / 131 (1.53%)	
occurrences causally related to treatment / all	2 / 8	0 / 2	
deaths causally related to treatment / all	1 / 6	0 / 2	
Hepatic function abnormal			
subjects affected / exposed	5 / 261 (1.92%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	2 / 5	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatic pain			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatorenal syndrome			
subjects affected / exposed	1 / 261 (0.38%)	2 / 131 (1.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Hyperbilirubinaemia			
subjects affected / exposed	4 / 261 (1.53%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	2 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	0 / 261 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			

subjects affected / exposed	1 / 261 (0.38%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portal vein thrombosis			
subjects affected / exposed	1 / 261 (0.38%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute prerenal failure			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder dysplasia			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	0 / 261 (0.00%)	1 / 131 (0.76%)	
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 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive uropathy			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oliguria			

subjects affected / exposed	0 / 261 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 261 (0.38%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal failure acute			
subjects affected / exposed	4 / 261 (1.53%)	2 / 131 (1.53%)	
occurrences causally related to treatment / all	3 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric obstruction			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal mass			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothyroidism			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 261 (0.77%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	0 / 261 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Intervertebral disc protrusion			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint range of motion decreased			
subjects affected / exposed	0 / 261 (0.00%)	1 / 131 (0.76%)	
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	4 / 261 (1.53%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	3 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 261 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 261 (0.77%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	0 / 261 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
H1n1 influenza			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			

subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	3 / 261 (1.15%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral fungal infection			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis bacterial			
subjects affected / exposed	1 / 261 (0.38%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia			
subjects affected / exposed	3 / 261 (1.15%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sepsis			
subjects affected / exposed	0 / 261 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Septic shock			
subjects affected / exposed	0 / 261 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			

subjects affected / exposed	0 / 261 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculosis			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 261 (0.77%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Decreased appetite			
subjects affected / exposed	10 / 261 (3.83%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	10 / 12	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	6 / 261 (2.30%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	5 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid retention			

subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperammonaemia			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 261 (0.38%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Hypoglycaemia			
subjects affected / exposed	2 / 261 (0.77%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Hyponatraemia			
subjects affected / exposed	4 / 261 (1.53%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	2 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	1 / 261 (0.38%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Brivanib	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	250 / 261 (95.79%)	111 / 131 (84.73%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	123 / 261 (47.13%)	18 / 131 (13.74%)	
occurrences (all)	159	21	
Hypotension			
subjects affected / exposed	14 / 261 (5.36%)	1 / 131 (0.76%)	
occurrences (all)	15	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	57 / 261 (21.84%)	24 / 131 (18.32%)	
occurrences (all)	72	26	
Fatigue			
subjects affected / exposed	122 / 261 (46.74%)	31 / 131 (23.66%)	
occurrences (all)	169	35	
Mucosal inflammation			
subjects affected / exposed	27 / 261 (10.34%)	4 / 131 (3.05%)	
occurrences (all)	30	4	
Pain			
subjects affected / exposed	16 / 261 (6.13%)	4 / 131 (3.05%)	
occurrences (all)	16	4	
Oedema peripheral			
subjects affected / exposed	39 / 261 (14.94%)	22 / 131 (16.79%)	
occurrences (all)	54	30	
Pyrexia			
subjects affected / exposed	32 / 261 (12.26%)	12 / 131 (9.16%)	
occurrences (all)	40	14	
Respiratory, thoracic and mediastinal disorders			
Dysphonia			
subjects affected / exposed	56 / 261 (21.46%)	2 / 131 (1.53%)	
occurrences (all)	70	3	
Cough			
subjects affected / exposed	38 / 261 (14.56%)	16 / 131 (12.21%)	
occurrences (all)	41	16	

Dyspnoea			
subjects affected / exposed	36 / 261 (13.79%)	14 / 131 (10.69%)	
occurrences (all)	43	15	
Epistaxis			
subjects affected / exposed	14 / 261 (5.36%)	3 / 131 (2.29%)	
occurrences (all)	18	3	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	27 / 261 (10.34%)	11 / 131 (8.40%)	
occurrences (all)	33	11	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	40 / 261 (15.33%)	8 / 131 (6.11%)	
occurrences (all)	49	10	
Aspartate aminotransferase increased			
subjects affected / exposed	52 / 261 (19.92%)	18 / 131 (13.74%)	
occurrences (all)	58	19	
Weight decreased			
subjects affected / exposed	60 / 261 (22.99%)	9 / 131 (6.87%)	
occurrences (all)	66	9	
Weight increased			
subjects affected / exposed	7 / 261 (2.68%)	7 / 131 (5.34%)	
occurrences (all)	10	7	
Nervous system disorders			
Dizziness			
subjects affected / exposed	38 / 261 (14.56%)	8 / 131 (6.11%)	
occurrences (all)	44	9	
Dysgeusia			
subjects affected / exposed	19 / 261 (7.28%)	0 / 131 (0.00%)	
occurrences (all)	19	0	
Headache			
subjects affected / exposed	55 / 261 (21.07%)	11 / 131 (8.40%)	
occurrences (all)	66	11	
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	14 / 261 (5.36%)	6 / 131 (4.58%)	
occurrences (all)	15	6	
Thrombocytopenia			
subjects affected / exposed	27 / 261 (10.34%)	3 / 131 (2.29%)	
occurrences (all)	32	3	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	25 / 261 (9.58%)	13 / 131 (9.92%)	
occurrences (all)	27	15	
Abdominal pain			
subjects affected / exposed	69 / 261 (26.44%)	22 / 131 (16.79%)	
occurrences (all)	86	23	
Abdominal pain upper			
subjects affected / exposed	44 / 261 (16.86%)	14 / 131 (10.69%)	
occurrences (all)	49	18	
Constipation			
subjects affected / exposed	50 / 261 (19.16%)	19 / 131 (14.50%)	
occurrences (all)	70	21	
Ascites			
subjects affected / exposed	32 / 261 (12.26%)	15 / 131 (11.45%)	
occurrences (all)	34	16	
Dry mouth			
subjects affected / exposed	17 / 261 (6.51%)	4 / 131 (3.05%)	
occurrences (all)	19	4	
Diarrhoea			
subjects affected / exposed	120 / 261 (45.98%)	19 / 131 (14.50%)	
occurrences (all)	226	27	
Dyspepsia			
subjects affected / exposed	34 / 261 (13.03%)	4 / 131 (3.05%)	
occurrences (all)	36	4	
Nausea			
subjects affected / exposed	95 / 261 (36.40%)	27 / 131 (20.61%)	
occurrences (all)	133	31	
Stomatitis			
subjects affected / exposed	23 / 261 (8.81%)	1 / 131 (0.76%)	
occurrences (all)	24	1	

Vomiting			
subjects affected / exposed	81 / 261 (31.03%)	11 / 131 (8.40%)	
occurrences (all)	115	17	
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	33 / 261 (12.64%)	13 / 131 (9.92%)	
occurrences (all)	39	16	
Skin and subcutaneous tissue disorders			
Palmar-Plantar erythrodysaesthesia syndrome			
subjects affected / exposed	38 / 261 (14.56%)	9 / 131 (6.87%)	
occurrences (all)	45	9	
Pruritus			
subjects affected / exposed	26 / 261 (9.96%)	13 / 131 (9.92%)	
occurrences (all)	31	17	
Rash			
subjects affected / exposed	24 / 261 (9.20%)	9 / 131 (6.87%)	
occurrences (all)	31	9	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	27 / 261 (10.34%)	3 / 131 (2.29%)	
occurrences (all)	33	3	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	41 / 261 (15.71%)	3 / 131 (2.29%)	
occurrences (all)	42	3	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	14 / 261 (5.36%)	7 / 131 (5.34%)	
occurrences (all)	14	8	
Back pain			
subjects affected / exposed	29 / 261 (11.11%)	11 / 131 (8.40%)	
occurrences (all)	32	12	
Musculoskeletal pain			
subjects affected / exposed	15 / 261 (5.75%)	5 / 131 (3.82%)	
occurrences (all)	15	5	
Metabolism and nutrition disorders			

Decreased appetite			
subjects affected / exposed	155 / 261 (59.39%)	31 / 131 (23.66%)	
occurrences (all)	209	35	
Hyperkalaemia			
subjects affected / exposed	23 / 261 (8.81%)	3 / 131 (2.29%)	
occurrences (all)	29	3	
Hypoalbuminaemia			
subjects affected / exposed	29 / 261 (11.11%)	6 / 131 (4.58%)	
occurrences (all)	36	6	
Hyponatraemia			
subjects affected / exposed	52 / 261 (19.92%)	10 / 131 (7.63%)	
occurrences (all)	78	13	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 September 2009	Includes a change in the efficacy criteria to Modified RECIST for HCC, addition of an independent radiology vendor, updates to CYP3 data and other administrative issues.
29 June 2010	Increase patient number by up to 75 patients for timeline mitigation due to slower than expected event rate
10 February 2011	Includes changes for the optional long term open label extension (LTOLE) portion of the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported