



Clinical trial results:

A Randomized, Double-blind, Multicenter Phase III Study of Brivanib versus Placebo as Adjuvant Therapy to Trans-Arterial Chemo-Embolization (TACE) in Patients with Unresectable Hepatocellular Carcinoma: The BRISK TA Study

Summary

EudraCT number	2008-008715-26
Trial protocol	FR ES IT
Global end of trial date	26 January 2018

Results information

Result version number	v1 (current)
This version publication date	01 March 2019
First version publication date	01 March 2019

Trial information

Trial identification

Sponsor protocol code	CA182-037
-----------------------	-----------

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,
Public contact	EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, 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	28 September 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 September 2012
Global end of trial reached?	Yes
Global end of trial date	26 January 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to compare the overall survival (OS) of hepatocellular carcinoma (HCC) subjects who receive brivanib as adjuvant treatments to TACE therapy, with the OS of HCC subjects who receive matched placebo with TACE therapy.

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	20 July 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	Canada: 2
Country: Number of subjects enrolled	France: 32
Country: Number of subjects enrolled	Hong Kong: 4
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Japan: 78
Country: Number of subjects enrolled	Korea, Republic of: 68
Country: Number of subjects enrolled	China: 244
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	Taiwan: 28
Country: Number of subjects enrolled	Thailand: 12
Country: Number of subjects enrolled	United States: 18
Worldwide total number of subjects	502
EEA total number of subjects	45

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)	343
From 65 to 84 years	159
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

734 participants were enrolled in the study and 502 were randomized. Of the 232 not randomized, 10 had adverse events, 9 withdrew consent, 1 died, 17 no longer met study criteria, 1 due to administrative reasons by sponsor, 10 due to other reasons and 184 did not qualify for TACE population.

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, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo, by mouth, once daily after each TACE procedure

Arm type	Placebo
Investigational medicinal product name	Placebo for BMS-582664-02
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

800 mg (4X 200 mg film coated tablet), by mouth once daily

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

Arm description:

Brivanib 800 mg by mouth, once daily after each TACE procedure

Arm type	Experimental
Investigational medicinal product name	BMS-582664-02
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

800 mg (4X 200 mg film coated tablet), by mouth once daily

Number of subjects in period 1	Placebo	Brivanib
Started	253	249
Completed	3	57
Not completed	250	192
Subject request to discontinue treatment	14	25
Adverse event, serious fatal	-	2
Disease progression	91	45
Others	7	3
Maximum clinical benefit	6	3
No longer meets study criteria	2	1
Consent withdrawn by subject	1	5
Adverse event, non-fatal	22	22
Study drug toxicity	6	65
Investigator decision	2	1
Transfer to systemic cancer therapy	2	-
Physician judgement	-	3
Poor/non-compliance	5	5
Administrative reason by sponsor	92	12

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description: Placebo, by mouth, once daily after each TACE procedure	
Reporting group title	Brivanib
Reporting group description: Brivanib 800 mg by mouth, once daily after each TACE procedure	

Reporting group values	Placebo	Brivanib	Total
Number of subjects	253	249	502
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)	170	173	343
From 65-84 years	83	76	159
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	58.3	57.2	
standard deviation	± 12.42	± 13.02	-
Sex: Female, Male Units: Subjects			
Female	37	43	80
Male	216	206	422
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	223	218	441
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	2	3
White	28	28	56
More than one race	0	0	0
Unknown or Not Reported	1	1	2

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo, by mouth, once daily after each TACE procedure	
Reporting group title	Brivanib
Reporting group description:	
Brivanib 800 mg by mouth, once daily after each TACE procedure	

Primary: Overall Survival (OS) - Univariate analysis; Brivanib vs placebo

End point title	Overall Survival (OS) - Univariate analysis; Brivanib vs placebo
End point description:	
Overall Survival, OS: defined as the time from randomization to death from any cause. Subjects who did not die were censored at the last known alive date. Here, '99999' signifies data not available for this endpoint.	
End point type	Primary
End point timeframe:	
Assessed from from the date of randomization to the date of death from any cause.	

End point values	Placebo	Brivanib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	253	249		
Units: Months				
median (confidence interval 95%)				
OS	26.1 (19.0 to 30.9)	26.4 (19.1 to 9999)		

Statistical analyses

Statistical analysis title	Kaplan-Meier Analysis of OS - Randomized Subjects
Comparison groups	Placebo v Brivanib
Number of subjects included in analysis	502
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5289
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.23

Secondary: Time-to-disease progression (TTDP)

End point title	Time-to-disease progression (TTDP)
-----------------	------------------------------------

End point description:

TTDP is defined for all randomized patients as the time from the date of the first TACE to the date the disease progresses to an advanced stage during the course of TACE therapy as determined by the occurrence of any one of the following events: • Development of extrahepatic metastasis. • Development of vascular invasion. • Death • Deterioration of liver function to Child-Pugh Class C. • Deterioration of ECOG performance status by 2 points if liver disease related OR, if not liver disease related, deterioration of ECOG performance status by 2 points AND lasting > 2 weeks in duration. Subjects without any progression events and who did not die were censored at the last date of assessment date. Analysis was performed on all subjects who were randomized to any treatment.

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

End point timeframe:

From the first TACE and then every 8 weeks

End point values	Placebo	Brivanib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	253	249		
Units: Months				
median (confidence interval 95%)				
TTDP	10.9 (8.4 to 14.4)	12.0 (9.5 to 15.3)		

Statistical analyses

Statistical analysis title	Kaplan-Meier Analysis of TTDP
Comparison groups	Placebo v Brivanib
Number of subjects included in analysis	502
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6209
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.22

Secondary: Time to Extrahepatic Spread or Vascular Invasion

End point title	Time to Extrahepatic Spread or Vascular Invasion
-----------------	--------------------------------------------------

End point description:

Time to extrahepatic spread or vascular invasion is defined as the time from the date of the first TACE to the date extrahepatic spread or vascular invasion was documented, whichever comes first. Subjects without any progression events and who did not die were censored at the last date of assessment date. Analysis was performed on all subjects who were randomized to any treatment.

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

End point timeframe:

From the date of the first TACE to the date extrahepatic spread or vascular invasion was documented

End point values	Placebo	Brivanib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	253	249		
Units: Months				
median (confidence interval 95%)				
TTES or VI	24.9 (13.8 to 9999)	9999 (17.6 to 9999)		

Statistical analyses

Statistical analysis title	K-M Analysis of Time to Extrahepatic Spread
Comparison groups	Placebo v Brivanib
Number of subjects included in analysis	502
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0096
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	0.9

Secondary: Rate of TACE Sessions

End point title	Rate of TACE Sessions
-----------------	-----------------------

End point description:

The total number of TACE procedures is defined for all randomized subjects as the number of TACE procedures the patient received between randomization and the time of event or censoring of TTDP. All TACE procedures were counted as separate events whatever the reason for repeating the procedure. The TACE procedure performed prior to randomization was not counted.

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

End point timeframe:

From randomization and the time of event or censoring of the main secondary endpoint Time-To-Disease Progression

End point values	Placebo	Brivanib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	253	249		
Units: Number				
arithmetic mean (standard deviation)				
TACE Procedures prior to DP / censoring	1.47 (± 1.717)	1.10 (± 1.840)		
TACE Procedures, all	1.96 (± 1.861)	1.37 (± 2.008)		

Statistical analyses

Statistical analysis title	Rate of TACE sessions
Comparison groups	Placebo v Brivanib
Number of subjects included in analysis	502
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002
Method	Andersen-Gill Model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	0.86

Secondary: Number of subjects with Adverse events (AEs), Drug related AEs. Serious adverse events (SAEs), Treatment related SAEs, AEs leading to discontinuation, AEs of special interest (AEOSI) and death

End point title	Number of subjects with Adverse events (AEs), Drug related AEs. Serious adverse events (SAEs), Treatment related SAEs, AEs leading to discontinuation, AEs of special interest (AEOSI) and death
-----------------	--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

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 and may or may not be related to treatment. SAE=an untoward 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. Drug-related=having certain, probable, possible, or missing relationship to study drug. Analysis was performed in all treated subjects.

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

End point timeframe:

All non-serious adverse events (NSAEs) and SAEs, were reported from first dose to 14 days and 30 days post final dose respectively

End point values	Placebo	Brivanib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	253	249		
Units: Subjects				
SAEs	94	118		
Related SAEs	9	56		
AEs leading to discontinuation	46	98		
>= Grade 3 AEs	128	221		
AEOSI - Arterial Thromboembolic	3	0		
AEOSI - Hepatic	130	137		
AEOSI - Hypertension	30	116		
AEOSI - Hyponatremia	27	71		
AEOSI - Hypothyroidism	18	66		
AEOSI - Proteinuria	28	76		
AEOSI - RPL Syndrome	0	1		
Death	12	18		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Grade 3-4 Abnormalities on Laboratory Test Results

End point title	Number of Participants With Grade 3-4 Abnormalities on Laboratory Test Results
-----------------	--------------------------------------------------------------------------------

End point description:

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

End point timeframe:

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; ULN=upper limit of normal. Here, 'n' represents number of subjects evaluable for each category.

End point values	Placebo	Brivanib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	253	246		
Units: Subjects				
Absolute neutrophil count (n=252,244)	19	26		
Hemoglobin (n=252,244)	12	6		
Leukocytes (n=252,244)	12	22		
Neutrophils (n=238,230)	17	26		
Platelet count (n=252,244)	19	40		
ALT (n=252,244)	39	46		
ALP (n=250,243)	9	4		

AST (n=252,244)	58	60		
Bilirubin Total (n=252,244)	17	25		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with percent reduction from baseline and on-study Left Ventricular Ejection Fraction (LVEF) <10%, 10%-<=20% and 20%-<40%

End point title	Number of subjects with percent reduction from baseline and on-study Left Ventricular Ejection Fraction (LVEF) <10%, 10%-<=20% and 20%-<40%
-----------------	---------------------------------------------------------------------------------------------------------------------------------------------

End point description:

A single 12-lead electrocardiogram was performed. The analysis was performed for on-study subjects with available reduction. Here, 'number of subjects analysed' represents number of subjects evaluable for this endpoint.

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

End point timeframe:

At baseline, 12 weeks after start of treatment, and thereafter whenever clinically indicated

End point values	Placebo	Brivanib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	192	169		
Units: Subjects				
<10%	161	134		
10%-<20%	31	33		
20%-<40%	0	2		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All non-serious adverse events (NSAEs) and serious adverse events (SAEs) were reported from first dose to 14 days and 30 days post final dose respectively.

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

Dictionary used

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

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

Reporting groups

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

Reporting group description:

Subjects received Brivanib alaninate matching placebo as oral tablets once daily until the criteria for discontinuation of subjects from treatment was met.

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

Reporting group description:

Subjects received 800 milligram (mg) Brivanib alaninate as oral tablets (each tablet of 200 mg * 4) once daily until the criteria for discontinuation of subjects from treatment was met.

Serious adverse events	Placebo	Brivanib	
Total subjects affected by serious adverse events			
subjects affected / exposed	94 / 253 (37.15%)	118 / 246 (47.97%)	
number of deaths (all causes)	12	18	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenoma benign			
subjects affected / exposed	1 / 253 (0.40%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	1 / 253 (0.40%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric cancer			
subjects affected / exposed	1 / 253 (0.40%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cancer metastatic			

subjects affected / exposed	0 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic neoplasm malignant			
subjects affected / exposed	8 / 253 (3.16%)	6 / 246 (2.44%)	
occurrences causally related to treatment / all	0 / 8	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic neoplasm malignant recurrent			
subjects affected / exposed	0 / 253 (0.00%)	1 / 246 (0.41%)	
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	2 / 253 (0.79%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	38 / 253 (15.02%)	15 / 246 (6.10%)	
occurrences causally related to treatment / all	0 / 40	0 / 17	
deaths causally related to treatment / all	0 / 12	0 / 3	
Neoplasm			
subjects affected / exposed	1 / 253 (0.40%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatic adenoma			
subjects affected / exposed	1 / 253 (0.40%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	1 / 253 (0.40%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Tumour thrombosis			

subjects affected / exposed	1 / 253 (0.40%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 253 (0.00%)	4 / 246 (1.63%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	0 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 253 (0.40%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	2 / 253 (0.79%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 253 (0.40%)	3 / 246 (1.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 3	
Fatigue			
subjects affected / exposed	3 / 253 (1.19%)	3 / 246 (1.22%)	
occurrences causally related to treatment / all	1 / 3	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 253 (0.00%)	2 / 246 (0.81%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hernia			
subjects affected / exposed	1 / 253 (0.40%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	0 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	0 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Oedema peripheral			
subjects affected / exposed	2 / 253 (0.79%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	5 / 253 (1.98%)	6 / 246 (2.44%)	
occurrences causally related to treatment / all	1 / 5	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 253 (0.40%)	0 / 246 (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	2 / 253 (0.79%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiccups			
subjects affected / exposed	2 / 253 (0.79%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 253 (0.40%)	0 / 246 (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	0 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	0 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 253 (0.00%)	2 / 246 (0.81%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 253 (0.00%)	2 / 246 (0.81%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	0 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood urea increased			
subjects affected / exposed	0 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			
subjects affected / exposed	0 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	0 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 253 (0.40%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	0 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb traumatic amputation			
subjects affected / exposed	1 / 253 (0.40%)	0 / 246 (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	5 / 253 (1.98%)	3 / 246 (1.22%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 253 (0.40%)	0 / 246 (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	1 / 253 (0.40%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	0 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound			
subjects affected / exposed	1 / 253 (0.40%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Hydrocele			
subjects affected / exposed	0 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure			
subjects affected / exposed	0 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 253 (0.40%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Carpal tunnel syndrome			

subjects affected / exposed	0 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	1 / 253 (0.40%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia			
subjects affected / exposed	1 / 253 (0.40%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 253 (0.00%)	2 / 246 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Grand mal convulsion			
subjects affected / exposed	0 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	0 / 253 (0.00%)	3 / 246 (1.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Headache			
subjects affected / exposed	0 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			

subjects affected / exposed	2 / 253 (0.79%)	5 / 246 (2.03%)	
occurrences causally related to treatment / all	0 / 3	2 / 9	
deaths causally related to treatment / all	0 / 1	0 / 0	
Loss of consciousness			
subjects affected / exposed	0 / 253 (0.00%)	1 / 246 (0.41%)	
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	0 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord infarction			
subjects affected / exposed	1 / 253 (0.40%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 253 (0.40%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypersplenism			
subjects affected / exposed	1 / 253 (0.40%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			

subjects affected / exposed	0 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			
subjects affected / exposed	1 / 253 (0.40%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 253 (0.00%)	3 / 246 (1.22%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 253 (0.00%)	2 / 246 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	4 / 253 (1.58%)	6 / 246 (2.44%)	
occurrences causally related to treatment / all	0 / 6	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 253 (0.40%)	2 / 246 (0.81%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	1 / 253 (0.40%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			

subjects affected / exposed	6 / 253 (2.37%)	8 / 246 (3.25%)	
occurrences causally related to treatment / all	0 / 6	3 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 253 (0.40%)	2 / 246 (0.81%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	0 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food poisoning			
subjects affected / exposed	0 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric polyps			
subjects affected / exposed	1 / 253 (0.40%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	0 / 253 (0.00%)	2 / 246 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 253 (0.40%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			
subjects affected / exposed	0 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Irritable bowel syndrome			

subjects affected / exposed	0 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth haemorrhage			
subjects affected / exposed	0 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	2 / 253 (0.79%)	2 / 246 (0.81%)	
occurrences causally related to treatment / all	0 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal varices haemorrhage			
subjects affected / exposed	1 / 253 (0.40%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 253 (0.40%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 253 (0.40%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 253 (0.40%)	5 / 246 (2.03%)	
occurrences causally related to treatment / all	0 / 2	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Varices oesophageal			
subjects affected / exposed	2 / 253 (0.79%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Volvulus			

subjects affected / exposed	1 / 253 (0.40%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 253 (0.79%)	3 / 246 (1.22%)	
occurrences causally related to treatment / all	0 / 2	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	1 / 253 (0.40%)	2 / 246 (0.81%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stone			
subjects affected / exposed	1 / 253 (0.40%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biloma			
subjects affected / exposed	2 / 253 (0.79%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	0 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	2 / 253 (0.79%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 253 (0.40%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			

subjects affected / exposed	2 / 253 (0.79%)	4 / 246 (1.63%)	
occurrences causally related to treatment / all	1 / 2	2 / 4	
deaths causally related to treatment / all	1 / 2	0 / 1	
Hepatic function abnormal			
subjects affected / exposed	1 / 253 (0.40%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic haemorrhage			
subjects affected / exposed	0 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic necrosis			
subjects affected / exposed	0 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic pain			
subjects affected / exposed	0 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	2 / 253 (0.79%)	4 / 246 (1.63%)	
occurrences causally related to treatment / all	0 / 2	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	1 / 253 (0.40%)	2 / 246 (0.81%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			
subjects affected / exposed	0 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Palmar-Plantar erythrodysesthesia syndrome			

subjects affected / exposed	0 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic skin eruption			
subjects affected / exposed	0 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrotic syndrome			
subjects affected / exposed	0 / 253 (0.00%)	3 / 246 (1.22%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Proteinuria			
subjects affected / exposed	0 / 253 (0.00%)	3 / 246 (1.22%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	1 / 253 (0.40%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal injury			
subjects affected / exposed	0 / 253 (0.00%)	1 / 246 (0.41%)	
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 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 253 (0.79%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Spinal column stenosis			
subjects affected / exposed	0 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	1 / 253 (0.40%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal infection			
subjects affected / exposed	1 / 253 (0.40%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
subjects affected / exposed	1 / 253 (0.40%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary tract infection			
subjects affected / exposed	0 / 253 (0.00%)	2 / 246 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 253 (0.40%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			

subjects affected / exposed	0 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic infection			
subjects affected / exposed	1 / 253 (0.40%)	0 / 246 (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	0 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected skin ulcer			
subjects affected / exposed	0 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious peritonitis			
subjects affected / exposed	0 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Liver abscess			

subjects affected / exposed	2 / 253 (0.79%)	2 / 246 (0.81%)	
occurrences causally related to treatment / all	0 / 4	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	0 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis			
subjects affected / exposed	0 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral candidiasis			
subjects affected / exposed	0 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media chronic			
subjects affected / exposed	0 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis bacterial			
subjects affected / exposed	1 / 253 (0.40%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 253 (0.40%)	2 / 246 (0.81%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	1 / 253 (0.40%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			

subjects affected / exposed	1 / 253 (0.40%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Tuberculosis			
subjects affected / exposed	0 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculous pleurisy			
subjects affected / exposed	1 / 253 (0.40%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 253 (0.40%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 253 (0.79%)	5 / 246 (2.03%)	
occurrences causally related to treatment / all	2 / 2	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid retention			
subjects affected / exposed	0 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 253 (0.40%)	0 / 246 (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	0 / 253 (0.00%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoalbuminaemia			
subjects affected / exposed	1 / 253 (0.40%)	1 / 246 (0.41%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypochloraemia			
subjects affected / exposed	1 / 253 (0.40%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 253 (0.40%)	3 / 246 (1.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 253 (0.40%)	0 / 246 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 253 (0.40%)	3 / 246 (1.22%)	
occurrences causally related to treatment / all	0 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoproteinaemia			
subjects affected / exposed	1 / 253 (0.40%)	3 / 246 (1.22%)	
occurrences causally related to treatment / all	0 / 1	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sodium retention			
subjects affected / exposed	0 / 253 (0.00%)	1 / 246 (0.41%)	
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	Placebo	Brivanib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	236 / 253 (93.28%)	241 / 246 (97.97%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	29 / 253 (11.46%)	115 / 246 (46.75%)	
occurrences (all)	43	169	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	5 / 253 (1.98%)	18 / 246 (7.32%)	
occurrences (all)	5	32	
Fatigue			
subjects affected / exposed	58 / 253 (22.92%)	100 / 246 (40.65%)	
occurrences (all)	80	138	
Oedema peripheral			
subjects affected / exposed	17 / 253 (6.72%)	40 / 246 (16.26%)	
occurrences (all)	17	51	
Pain			
subjects affected / exposed	15 / 253 (5.93%)	14 / 246 (5.69%)	
occurrences (all)	22	17	
Pyrexia			
subjects affected / exposed	114 / 253 (45.06%)	89 / 246 (36.18%)	
occurrences (all)	207	173	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	19 / 253 (7.51%)	31 / 246 (12.60%)	
occurrences (all)	24	43	
Dyspnoea			
subjects affected / exposed	8 / 253 (3.16%)	17 / 246 (6.91%)	
occurrences (all)	9	21	
Dysphonia			
subjects affected / exposed	5 / 253 (1.98%)	45 / 246 (18.29%)	
occurrences (all)	7	59	
Epistaxis			

subjects affected / exposed	4 / 253 (1.58%)	20 / 246 (8.13%)	
occurrences (all)	6	23	
Oropharyngeal pain			
subjects affected / exposed	4 / 253 (1.58%)	21 / 246 (8.54%)	
occurrences (all)	5	24	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	25 / 253 (9.88%)	30 / 246 (12.20%)	
occurrences (all)	33	36	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	84 / 253 (33.20%)	87 / 246 (35.37%)	
occurrences (all)	148	162	
Aspartate aminotransferase increased			
subjects affected / exposed	95 / 253 (37.55%)	84 / 246 (34.15%)	
occurrences (all)	157	141	
Blood albumin decreased			
subjects affected / exposed	15 / 253 (5.93%)	21 / 246 (8.54%)	
occurrences (all)	21	29	
Blood alkaline phosphatase increased			
subjects affected / exposed	28 / 253 (11.07%)	23 / 246 (9.35%)	
occurrences (all)	39	39	
Blood bilirubin increased			
subjects affected / exposed	11 / 253 (4.35%)	15 / 246 (6.10%)	
occurrences (all)	16	22	
Blood thyroid stimulating hormone increased			
subjects affected / exposed	5 / 253 (1.98%)	30 / 246 (12.20%)	
occurrences (all)	5	31	
Gamma-Glutamyltransferase increased			
subjects affected / exposed	34 / 253 (13.44%)	32 / 246 (13.01%)	
occurrences (all)	49	50	
Haemoglobin decreased			
subjects affected / exposed	19 / 253 (7.51%)	23 / 246 (9.35%)	
occurrences (all)	21	37	
International normalised ratio			

increased			
subjects affected / exposed	16 / 253 (6.32%)	22 / 246 (8.94%)	
occurrences (all)	24	29	
Neutrophil count decreased			
subjects affected / exposed	29 / 253 (11.46%)	31 / 246 (12.60%)	
occurrences (all)	64	58	
Platelet count decreased			
subjects affected / exposed	42 / 253 (16.60%)	58 / 246 (23.58%)	
occurrences (all)	103	112	
Prothrombin time prolonged			
subjects affected / exposed	10 / 253 (3.95%)	16 / 246 (6.50%)	
occurrences (all)	12	17	
Weight decreased			
subjects affected / exposed	11 / 253 (4.35%)	20 / 246 (8.13%)	
occurrences (all)	11	23	
White blood cell count decreased			
subjects affected / exposed	48 / 253 (18.97%)	53 / 246 (21.54%)	
occurrences (all)	103	123	
White blood cell count increased			
subjects affected / exposed	13 / 253 (5.14%)	13 / 246 (5.28%)	
occurrences (all)	17	15	
Nervous system disorders			
Dizziness			
subjects affected / exposed	8 / 253 (3.16%)	34 / 246 (13.82%)	
occurrences (all)	8	45	
Headache			
subjects affected / exposed	15 / 253 (5.93%)	39 / 246 (15.85%)	
occurrences (all)	16	55	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	7 / 253 (2.77%)	15 / 246 (6.10%)	
occurrences (all)	10	22	
Thrombocytopenia			
subjects affected / exposed	11 / 253 (4.35%)	25 / 246 (10.16%)	
occurrences (all)	19	36	
Gastrointestinal disorders			

Abdominal discomfort subjects affected / exposed occurrences (all)	3 / 253 (1.19%) 5	14 / 246 (5.69%) 20	
Abdominal distension subjects affected / exposed occurrences (all)	25 / 253 (9.88%) 29	35 / 246 (14.23%) 52	
Abdominal pain subjects affected / exposed occurrences (all)	101 / 253 (39.92%) 188	88 / 246 (35.77%) 182	
Abdominal pain upper subjects affected / exposed occurrences (all)	35 / 253 (13.83%) 64	43 / 246 (17.48%) 78	
Constipation subjects affected / exposed occurrences (all)	41 / 253 (16.21%) 49	37 / 246 (15.04%) 57	
Ascites subjects affected / exposed occurrences (all)	16 / 253 (6.32%) 17	39 / 246 (15.85%) 51	
Dyspepsia subjects affected / exposed occurrences (all)	7 / 253 (2.77%) 7	17 / 246 (6.91%) 23	
Diarrhoea subjects affected / exposed occurrences (all)	25 / 253 (9.88%) 28	88 / 246 (35.77%) 171	
Nausea subjects affected / exposed occurrences (all)	67 / 253 (26.48%) 116	70 / 246 (28.46%) 115	
Stomatitis subjects affected / exposed occurrences (all)	3 / 253 (1.19%) 4	23 / 246 (9.35%) 34	
Vomiting subjects affected / exposed occurrences (all)	56 / 253 (22.13%) 92	63 / 246 (25.61%) 106	
Hepatobiliary disorders Hepatic pain			

subjects affected / exposed occurrences (all)	10 / 253 (3.95%) 15	14 / 246 (5.69%) 23	
Hyperbilirubinaemia subjects affected / exposed occurrences (all)	57 / 253 (22.53%) 102	57 / 246 (23.17%) 121	
Skin and subcutaneous tissue disorders Palmar-Plantar erythrodysesthesia syndrome subjects affected / exposed occurrences (all)	5 / 253 (1.98%) 5	77 / 246 (31.30%) 138	
Pruritus subjects affected / exposed occurrences (all)	14 / 253 (5.53%) 15	14 / 246 (5.69%) 21	
Rash subjects affected / exposed occurrences (all)	13 / 253 (5.14%) 16	24 / 246 (9.76%) 34	
Renal and urinary disorders Proteinuria subjects affected / exposed occurrences (all)	24 / 253 (9.49%) 29	69 / 246 (28.05%) 109	
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	18 / 253 (7.11%) 19	66 / 246 (26.83%) 74	
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	20 / 253 (7.91%) 21	16 / 246 (6.50%) 22	
Musculoskeletal pain subjects affected / exposed occurrences (all)	10 / 253 (3.95%) 13	14 / 246 (5.69%) 20	
Pain in extremity subjects affected / exposed occurrences (all)	3 / 253 (1.19%) 3	16 / 246 (6.50%) 23	
Infections and infestations Nasopharyngitis			

subjects affected / exposed	6 / 253 (2.37%)	15 / 246 (6.10%)	
occurrences (all)	7	24	
Upper respiratory tract infection			
subjects affected / exposed	8 / 253 (3.16%)	13 / 246 (5.28%)	
occurrences (all)	9	18	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	55 / 253 (21.74%)	105 / 246 (42.68%)	
occurrences (all)	76	149	
Hyperglycaemia			
subjects affected / exposed	17 / 253 (6.72%)	11 / 246 (4.47%)	
occurrences (all)	22	14	
Hyperkalaemia			
subjects affected / exposed	7 / 253 (2.77%)	16 / 246 (6.50%)	
occurrences (all)	7	21	
Hypoalbuminaemia			
subjects affected / exposed	33 / 253 (13.04%)	54 / 246 (21.95%)	
occurrences (all)	46	92	
Hypokalaemia			
subjects affected / exposed	20 / 253 (7.91%)	22 / 246 (8.94%)	
occurrences (all)	24	28	
Hyponatraemia			
subjects affected / exposed	26 / 253 (10.28%)	65 / 246 (26.42%)	
occurrences (all)	37	89	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported