Clinical trial results:
Phase 2, Open-label Single-Arm, Multi-Center Study to Evaluate the Efficacy and Safety of AMG 386 and Sorafenib as First Line Therapy for Subjects with Advanced or Inoperable Hepatocellular Carcinoma.

Summary

EudraCT number	2008-006212-38
Trial protocol	FR DE
Global end of trial date	08 June 2015

Results information

Result version number	v1 (current)
This version publication date	18 June 2016
First version publication date	18 June 2016

Trial information

Trial identification

Sponsor protocol code	20080580

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00872014
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Amgen, Inc.
Sponsor organisation address	One Amgen Center Drive, Thousand Oaks, CA, United States, 91320
Public contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com
Scientific contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.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	08 June 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to determine the efficacy of trebananib (AMG 386) in combination with sorafenib as measured by the time to progression event rate at 4-months in subjects with advanced or inoperable hepatocellular carcinoma (HCC).

Protection of trial subjects:

This study has been conducted in accordance with FDA country-specific national and local laws and with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines.
A copy of the protocol, proposed informed consent form, other written subject information, and any proposed advertising materials were submitted to the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) for written approval. A copy of the written approval of the protocol and informed consent form must have been received by Amgen before recruitment of subjects into the study and shipment of trebananib.
All subjects provided written informed consent before undergoing any study-related procedures, including screening procedures.
In order to ensure subject safety, the study team reviewed safety and pharmacokinetic data, if available, after 10 and 20 subjects in cohort A had been enrolled, had received at least 1 infusion of trebananib and 1 oral dose of sorafenib, and had the opportunity to be followed for ≥ 4 weeks; and after 6, 12, and 20 subjects had been enrolled in cohort B, had received at least 1 infusion of trebananib and 1 oral dose of sorafenib, and had the opportunity to be followed for ≥ 4 weeks.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 August 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	48 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 26
Country: Number of subjects enrolled	Australia: 9
Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	Germany: 15
Worldwide total number of subjects	60
EEA total number of subjects	25

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)	39
From 65 to 84 years	21
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 15 centers in Australia, France, Germany, and the United States. The first patient was enrolled on 26 August 2009 and the last patient enrolled on 21 June 2011.

Pre-assignment

Screening details:

A total of 90 subjects were screened for enrollment and 60 subjects enrolled:
- Cohort A: trebananib 10 mg/kg QW and sorafenib 400 mg
- Cohort B: trebananib 15 mg/kg QW and sorafenib 400 mg

The 2 cohorts were enrolled sequentially. Enrollment into cohort B commenced after a safety review for cohort A was completed (after 10 subjects enrolled).

Period 1

Period 1 title	Overall sudy (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Trebananib 10 mg/kg + Sorafenib

Arm description:

Participants received 10 mg/kg trebananib administered by intravenous infusion once a week in combination with sorafenib starting at 400 mg orally twice daily until disease progression, clinical progression, unacceptable toxicity, the subject withdrew consent or died.

Arm type	Experimental
Investigational medicinal product name	Trebananib
Investigational medicinal product code	AMG 386
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trebananib was administered intravenously once a week.

Investigational medicinal product name	Sorafenib
Investigational medicinal product code	
Other name	Nexavar®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Sorafenib was self-administered orally starting at 400 mg twice a day (BID).

Arm title	Trebananib 15 mg/kg + Sorafenib

Arm description:

Participants received 15 mg/kg trebananib administered by intravenous infusion once a week in combination with sorafenib starting at 400 mg orally twice daily until disease progression, clinical progression, unacceptable toxicity, the subject withdrew consent or died.

Arm type	Experimental
Investigational medicinal product name	Trebananib
Investigational medicinal product code	AMG 386
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details: Trebananib was administered intravenously once a week.	
Investigational medicinal product name	Sorafenib
Investigational medicinal product code	
Other name	Nexavar®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Sorafenib was self-administered orally starting at 400 mg twice a day (BID).

Number of subjects in period 1	Trebananib 10 mg/kg + Sorafenib	Trebananib 15 mg/kg + Sorafenib
Started	30	30
Completed	1	2
Not completed	29	28
Consent withdrawn by subject	1	3
Death	28	24
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Trebananib 10 mg/kg + Sorafenib
Reporting group description:	
Participants received 10 mg/kg trebananib administered by intravenous infusion once a week in combination with sorafenib starting at 400 mg orally twice daily until disease progression, clinical progression, unacceptable toxicity, the subject withdrew consent or died.	
Reporting group title	Trebananib 15 mg/kg + Sorafenib
Reporting group description:	
Participants received 15 mg/kg trebananib administered by intravenous infusion once a week in combination with sorafenib starting at 400 mg orally twice daily until disease progression, clinical progression, unacceptable toxicity, the subject withdrew consent or died.	

Reporting group values	Trebananib 10 mg/kg + Sorafenib	Trebananib 15 mg/kg + Sorafenib	Total
Number of subjects	30	30	60
Age categorical Units: Subjects			
< 65 years	17	22	39
≥ 65 years	13	8	21
Age continuous Units: years			
arithmetic mean	64.1	61.2	
standard deviation	± 9.2	± 9.8	-
Gender categorical Units: Subjects			
Female	7	3	10
Male	23	27	50
Race Units: Subjects			
White or Caucasian	23	19	42
Black or African American	0	4	4
Hispanic or Latino	2	2	4
Asian	3	5	8
Japanese	1	0	1
Native Hawaiian or Other Pacific Islander	1	0	1

End points

End points reporting groups

Reporting group title	Trebananib 10 mg/kg + Sorafenib

Reporting group description:

Participants received 10 mg/kg trebananib administered by intravenous infusion once a week in combination with sorafenib starting at 400 mg orally twice daily until disease progression, clinical progression, unacceptable toxicity, the subject withdrew consent or died.

Reporting group title	Trebananib 15 mg/kg + Sorafenib

Reporting group description:

Participants received 15 mg/kg trebananib administered by intravenous infusion once a week in combination with sorafenib starting at 400 mg orally twice daily until disease progression, clinical progression, unacceptable toxicity, the subject withdrew consent or died.

Primary: Progression-free Survival Rate at 4 Months

End point title	Progression-free Survival Rate at 4 Months[1]

End point description:

Progression-free survival rate at 4 months is defined as the Kaplan-Meier estimate of participants alive and without radiographic disease progression at 4 months.
Disease progression was based on the investigator's assessment of radiological assessments using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 with modifications. Participants alive and without progression at the time of the analysis data cut-off date were censored at the time of the last evaluable radiographic assessment.
Progressive disease (PD): At least a 20% increase in the size of target lesions, taking as reference the smallest size recorded since the treatment began, the appearance of one or more new lesions and/or unequivocal progression of any non-target lesions.

End point type	Primary

End point timeframe:

Progression-free survival rate at 4 months was analyzed after all participants completed follow-up; the median follow-up time was 69.1 weeks for cohort A and 44.6 weeks for cohort B.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypothesis was tested.

End point values	Trebananib 10 mg/kg + Sorafenib	Trebananib 15 mg/kg + Sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	30		
Units: percentage of participants				
number (confidence interval 80%)	58.6 (43.4 to 69.2)	57.1 (43.4 to 69.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events

End point title	Number of Participants with Adverse Events

End point description:

The National Cancer Institute, Common Terminology Criteria for Adverse Events (CTCAE), version 3.0, was used to assess the severity of adverse events according to the following:
Grade 1 = Mild, Grade 2 = Moderate, Grade 3 = Severe, Grade 4 = Life-threatening and Grade 5 = Death. The investigator assessed the relationship of each AE to trebabanib or sorafenib.
A serious adverse event (SAE) is defined as an adverse event that
- is fatal
- is life threatening (places the subject at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- other significant medical hazard

End point type	Secondary

End point timeframe:

From first dose until 30 days after last dose

End point values	Trebananib 10 mg/kg + Sorafenib	Trebananib 15 mg/kg + Sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	30		
Units: participants				
Any adverse event	30	30		
Grade ≥ 3	26	23		
Grade ≥ 4	7	11		
Fatal adverse events	4	4		
Serious adverse events	19	15		
Leading to discontinuation of trebananib	6	9		
Leading to sorafenib dose altered or withheld	19	17		
Treatment-related adverse events (TRAEs)	30	30		
TRAE grade ≥ 3	20	22		
TRAE grade ≥ 4	3	4		
Treatment-related fatal adverse events	1	2		
Treatment-related serious adverse events	12	10		
Trebananib-related adverse events	27	24		
Trebananib-related grade ≥ 3	12	15		
Trebananib-related grade ≥ 4	2	3		
Trebananib-related fatal adverse events	1	1		
Trebananib-related serious adverse events	11	9		
Sorafenib-related adverse events	30	29		
Sorafenib-related grade ≥ 3	19	21		
Sorafenib-related grade ≥ 4	2	4		
Sorafenib-related fatal adverse events	1	2		
Sorafenib-related serious adverse events	11	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate

End point title	Objective Response Rate

End point description:

Tumor response was based on radiological assessments using RECIST version 1.0 with modifications. An objective response is either a complete response or partial response confirmed by consecutive repeat assessments no less than 28 days after the criteria for response were first met.
Complete response (CR): Disappearance of all target and non-target lesions and no new lesions.
Partial response (PR): Disappearance of all target lesions with persistence of one or more non-target lesions and no new lesions, or, at least a 30% decrease in the size of target lesions, and no new lesions or unequivocal progression of non-target lesions.

End point type	Secondary

End point timeframe:

Tumor response was assessed every 8 weeks from day 1 of week 1 for 2 years, and then at least every 4 months thereafter; the median follow-up time was 69.1 weeks for cohort A and 44.6 weeks for cohort B.

End point values	Trebananib 10 mg/kg + Sorafenib	Trebananib 15 mg/kg + Sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	30		
Units: percentage of participants				
number (confidence interval 80%)	3.3 (0.4 to 12.4)	10 (3.7 to 20.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression

End point title	Time to Progression

End point description:

Time to progression (TTP) was defined as the time from the first dose of investigational product to disease progression. Subjects who did not meet the criteria for disease progression by the final analysis data cutoff date and subjects who died without evidence of radiographic disease progression were censored at their last evaluable disease assessment date. Time to progression was analyzed using the Kaplan-Meier method.

End point type	Secondary

End point timeframe:

Tumor response was assessed every 8 weeks from day 1 of week 1 for 2 years, and then at least every 4 months thereafter; the median follow-up time was 69.1 weeks for cohort A and 44.6 weeks for cohort B.

End point values	Trebananib 10 mg/kg + Sorafenib	Trebananib 15 mg/kg + Sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	30		
Units: months				
median (confidence interval 80%)	9 (3.6 to 12.6)	6.9 (3.6 to 9.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival

End point title	Progression-free Survival

End point description:

Progression-free survival (PFS) time is the time from the first dose to the first observed radiographic progression or death, whichever occurs first. Subjects alive and without progression at the time of the analysis data cutoff date were censored at the time of the last evaluable radiographic assessment. (PFS) time is the time from the first dose to the first observed radiographic
progression or death, whichever occurs first. Subjects alive and without progression at the time of the analysis data cutoff date were censored at the time of the last evaluable radiographic assessment. Progression-free survival was analyzed using the Kaplan-Meier method.

End point type	Secondary

End point timeframe:

Tumor response was assessed every 8 weeks from day 1 of week 1 for 2 years, and then at least every 4 months thereafter; the median follow-up time was 69.1 weeks for cohort A and 44.6 weeks for cohort B.

End point values	Trebananib 10 mg/kg + Sorafenib	Trebananib 15 mg/kg + Sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	30		
Units: months				
median (confidence interval 80%)	9 (3.5 to 11.1)	6.2 (3.7 to 9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate

End point title	Disease Control Rate

End point description:

Disease control rate is defined as a best response of at least stable disease on study with a duration of ≥ 16 weeks from study day 1 or a confirmed objective response, per RECIST v1.0 with modifications. Stable Disease (SD): Neither sufficient shrinkage of target lesions to qualify for PR nor sufficient increase of target lesions to qualify for PD, taking as reference the smallest lesion size, with no new lesions or unequivocal progression of non-target lesions.

End point type	Secondary

End point timeframe:

Tumor response was assessed every 8 weeks from day 1 of week 1 for 2 years, and then at least every 4 months thereafter; the median follow-up time was 69.1 weeks for cohort A and 44.6 weeks for cohort B.

End point values	Trebananib 10 mg/kg + Sorafenib	Trebananib 15 mg/kg + Sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	30		
Units: percentage of participnts				
number (confidence interval 80%)	50 (37 to 63)	46.7 (33.8 to 59.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

The time from the date of first dose to the date of death from any cause. Subjects who had not died by the analysis data cutoff date were censored at their last date known to be alive. Overall survival was analyzed
using the Kaplan-Meier method.

End point type	Secondary

End point timeframe:

The median follow-up time was 69.1 weeks for cohort A and 44.6 weeks for cohort B.

End point values	Trebananib 10 mg/kg + Sorafenib	Trebananib 15 mg/kg + Sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	30		
Units: months				
median (confidence interval 80%)	17 (9.8 to 22.5)	13.2 (7.3 to 16.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants who Developed Anti-trebananib Antibodies

End point title	Number of Participants who Developed Anti-trebananib Antibodies

End point description:

Samples were first tested in an electrochemiluminescence (ECL) immunoassay to detect antibodies capable of binding specifically to trebananib. Samples confirmed positive in the immunoassay were then tested in an ECL receptor-binding neutralizing antibody assay to measure the neutralizing or inhibitory effects of the antibodies in vitro. if a sample was positive in the immunoassay, but negative in the neutralizing assay, the subject was defined as positive for binding antibodies. If a sample was positive in both assays, a subject was defined as positive for neutralizing antibodies.
Developing antibody incidence is defined as subjects with a negative or no result at or before baseline and a positive result at a post-baseline time point.

End point type	Secondary

End point timeframe:

Blood samples were taken predose on day 1 of weeks 1, 5, and 9, and every 16 weeks thereafter until the safety follow-up visit.

End point values	Trebananib 10 mg/kg + Sorafenib	Trebananib 15 mg/kg + Sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[2]	26[3]		
Units: participants				
Developed Binding Antibodies	2	1		
Developed Neutralizing Antibodies	0	0		

Notes:

[2] - Subjects with at least one post-baseline immunoassay result

[3] - Subjects with at least one post-baseline immunoassay result

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Serum Concentration (Cmax) of Trebananib

End point title	Maximum Observed Serum Concentration (Cmax) of Trebananib

End point description:

Serum samples were analyzed for trebananib concentration using a validated enzyme linked immunosorbent assay (ELISA). The lower limit of quantification (LLOQ) of the serum assay was 20 ng/mL.

End point type	Secondary

End point timeframe:

Week 1, week 5, and week 9, at the end of infusion

End point values	Trebananib 10 mg/kg + Sorafenib	Trebananib 15 mg/kg + Sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	30		
Units: µg/mL				
arithmetic mean (standard deviation)				
Week 1 (N = 25, 30)	201 (± 89.3)	260 (± 122)		

Week 5 (N = 20, 19)	323 (± 115)	350 (± 135)		
Week 9 (N = 14, 19)	275 (± 105)	344 (± 104)		

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum Observed Serum Concentration (Cmin) of Trebananib

End point title	Minimum Observed Serum Concentration (Cmin) of Trebananib

End point description:

End point type	Secondary

End point timeframe:

Predose at week 2, week 5 and week 9

End point values	Trebananib 10 mg/kg + Sorafenib	Trebananib 15 mg/kg + Sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	25		
Units: µg/mL				
arithmetic mean (standard deviation)				
Week 2 (N = 27, 25)	10.2 (± 8.37)	12.7 (± 7.35)		
Week 5 (N = 20, 20)	18.2 (± 11.1)	25.5 (± 19.5)		
Week 9 (N = 15, 20)	15.7 (± 8.04)	31.5 (± 27.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum Observed Serum Concentration (Cmin) of Sorafenib

End point title	Minimum Observed Serum Concentration (Cmin) of Sorafenib

End point description:

Blood samples for sorafenib pharmacokinetics were taken from a subgroup of subjects at selected sites outside of Europe. Plasma concentrations of sorafenib were measured by a validated liquid chromatography–mass spectrometry (LC-MS/MS) method. The LLOQ was 10 ng/mL.

End point type	Secondary

End point timeframe:

Predose at weeks 2, 5 and 9

End point values	Trebananib 10 mg/kg + Sorafenib	Trebananib 15 mg/kg + Sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	9		
Units: µg/mL				
arithmetic mean (standard deviation)				
Week 2 (N = 5, 9)	5.85 (± 6.31)	5.25 (± 3.28)		
Week 5 (N = 4, 8)	8.11 (± 6.37)	2.8 (± 2.09)		
Week 9 (n = 3, 5)	6.26 (± 2.29)	3.35 (± 1.02)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose until 30 days after last dose.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Trebananib 15 mg/kg + Sorafenib

Reporting group description:

Participants received 15 mg/kg trebananib administered by intravenous infusion once a week in combination with sorafenib starting at 400 mg orally twice daily until disease progression, clinical progression, unacceptable toxicity, the subject withdrew consent or died.

Reporting group title	Trebananib 10 mg/kg + Sorafenib

Reporting group description:

Participants received 10 mg/kg trebananib administered by intravenous infusion once a week in combination with sorafenib starting at 400 mg orally twice daily until disease progression, clinical progression, unacceptable toxicity, the subject withdrew consent or died.

Serious adverse events	Trebananib 15 mg/kg + Sorafenib	Trebananib 10 mg/kg + Sorafenib	
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 30 (50.00%)	19 / 30 (63.33%)	
number of deaths (all causes)	25	28	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colorectal cancer			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular carcinoma			
subjects affected / exposed	3 / 30 (10.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 30 (0.00%)	2 / 30 (6.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hypertension			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Toe amputation			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 30 (0.00%)	3 / 30 (10.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 30 (0.00%)	2 / 30 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pain			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
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			
Choking			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dyspnoea			
subjects affected / exposed	1 / 30 (3.33%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung disorder			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pleural effusion			
subjects affected / exposed	1 / 30 (3.33%)	2 / 30 (6.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Mania			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
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	0 / 30 (0.00%)	2 / 30 (6.67%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			

subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound complication			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
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	1 / 30 (3.33%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal vein thrombosis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vision blurred			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (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	2 / 30 (6.67%)	3 / 30 (10.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocutaneous fistula			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			

subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Intestinal obstruction			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (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	0 / 30 (0.00%)	1 / 30 (3.33%)	
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	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Acute hepatic failure			

subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stone			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	4 / 30 (13.33%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	1 / 2	0 / 0	
Hepatorenal syndrome			
subjects affected / exposed	2 / 30 (6.67%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	2 / 30 (6.67%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Exfoliative rash			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Swelling face			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	1 / 30 (3.33%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
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 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis of male external genital organ			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			

subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
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 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (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 / 30 (3.33%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	0 / 30 (0.00%)	2 / 30 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 30 (3.33%)	2 / 30 (6.67%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			

subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (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	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Trebananib 15 mg/kg + Sorafenib	Trebananib 10 mg/kg + Sorafenib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 30 (100.00%)	30 / 30 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign neoplasm			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Colorectal cancer			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Metastatic pain			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Papilloma			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	

Tumour pain			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Haematoma			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Hypertension			
subjects affected / exposed	8 / 30 (26.67%)	10 / 30 (33.33%)	
occurrences (all)	13	14	
Peripheral ischaemia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Subclavian vein thrombosis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Venous thrombosis			
subjects affected / exposed	1 / 30 (3.33%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Surgical and medical procedures			
Cataract operation			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Abasia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Asthenia			
subjects affected / exposed	0 / 30 (0.00%)	10 / 30 (33.33%)	
occurrences (all)	0	28	
Chest pain			
subjects affected / exposed	0 / 30 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	

Chills			
subjects affected / exposed	1 / 30 (3.33%)	3 / 30 (10.00%)	
occurrences (all)	1	3	
Extravasation			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Face oedema			
subjects affected / exposed	1 / 30 (3.33%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Fatigue			
subjects affected / exposed	14 / 30 (46.67%)	16 / 30 (53.33%)	
occurrences (all)	21	46	
Feeling cold			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Gait disturbance			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
General physical health deterioration			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Generalised oedema			
subjects affected / exposed	1 / 30 (3.33%)	2 / 30 (6.67%)	
occurrences (all)	1	7	
Influenza like illness			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Localised oedema			
subjects affected / exposed	1 / 30 (3.33%)	2 / 30 (6.67%)	
occurrences (all)	1	2	
Malaise			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Mucosal inflammation			
subjects affected / exposed	2 / 30 (6.67%)	5 / 30 (16.67%)	
occurrences (all)	2	7	

Non-cardiac chest pain			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Oedema			
subjects affected / exposed	2 / 30 (6.67%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Oedema peripheral			
subjects affected / exposed	8 / 30 (26.67%)	8 / 30 (26.67%)	
occurrences (all)	10	12	
Pain			
subjects affected / exposed	2 / 30 (6.67%)	1 / 30 (3.33%)	
occurrences (all)	3	1	
Pyrexia			
subjects affected / exposed	4 / 30 (13.33%)	8 / 30 (26.67%)	
occurrences (all)	4	8	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 30 (3.33%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Reproductive system and breast disorders			
Balanoposthitis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Erectile dysfunction			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Genital lesion			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Penile pain			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Prostatitis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	3 / 30 (10.00%)	9 / 30 (30.00%)	
occurrences (all)	4	11	
Dysphonia			
subjects affected / exposed	1 / 30 (3.33%)	2 / 30 (6.67%)	
occurrences (all)	1	2	
Dyspnoea			
subjects affected / exposed	8 / 30 (26.67%)	9 / 30 (30.00%)	
occurrences (all)	8	19	
Dyspnoea at rest			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Dyspnoea exertional			
subjects affected / exposed	1 / 30 (3.33%)	3 / 30 (10.00%)	
occurrences (all)	1	3	
Epistaxis			
subjects affected / exposed	4 / 30 (13.33%)	1 / 30 (3.33%)	
occurrences (all)	5	1	
Oropharyngeal pain			
subjects affected / exposed	2 / 30 (6.67%)	2 / 30 (6.67%)	
occurrences (all)	2	2	
Pharyngeal erythema			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Pleural effusion			
subjects affected / exposed	1 / 30 (3.33%)	2 / 30 (6.67%)	
occurrences (all)	1	4	
Pleurisy			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Pleuritic pain			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Rhinorrhoea			
subjects affected / exposed	0 / 30 (0.00%)	3 / 30 (10.00%)	
occurrences (all)	0	3	

Sinus congestion			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Anxiety			
subjects affected / exposed	4 / 30 (13.33%)	6 / 30 (20.00%)	
occurrences (all)	4	6	
Bipolar disorder			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Confusional state			
subjects affected / exposed	2 / 30 (6.67%)	2 / 30 (6.67%)	
occurrences (all)	4	3	
Delirium			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Depression			
subjects affected / exposed	0 / 30 (0.00%)	6 / 30 (20.00%)	
occurrences (all)	0	6	
Insomnia			
subjects affected / exposed	3 / 30 (10.00%)	6 / 30 (20.00%)	
occurrences (all)	3	7	
Libido decreased			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Nervousness			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Sleep disorder			
subjects affected / exposed	1 / 30 (3.33%)	2 / 30 (6.67%)	
occurrences (all)	1	3	
Investigations			

Aspartate aminotransferase increased				
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)		
occurrences (all)	1	0		
Blood alkaline phosphatase increased				
subjects affected / exposed	1 / 30 (3.33%)	1 / 30 (3.33%)		
occurrences (all)	1	2		
Blood creatinine increased				
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)		
occurrences (all)	1	0		
Blood magnesium decreased				
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)		
occurrences (all)	1	0		
Blood pressure increased				
subjects affected / exposed	2 / 30 (6.67%)	0 / 30 (0.00%)		
occurrences (all)	2	0		
Blood urea decreased				
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)		
occurrences (all)	0	1		
Blood urea increased				
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)		
occurrences (all)	1	0		
Blood uric acid increased				
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)		
occurrences (all)	0	1		
Blood urine present				
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)		
occurrences (all)	0	1		
Breath sounds abnormal				
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)		
occurrences (all)	1	0		
C-reactive protein increased				
subjects affected / exposed	1 / 30 (3.33%)	1 / 30 (3.33%)		
occurrences (all)	1	1		
Culture urine positive				

subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
International normalised ratio increased			
subjects affected / exposed	1 / 30 (3.33%)	2 / 30 (6.67%)	
occurrences (all)	1	2	
Intraocular pressure increased			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Lipase increased			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Platelet count decreased			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	2	
Transaminases increased			
subjects affected / exposed	2 / 30 (6.67%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Urine output decreased			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Weight decreased			
subjects affected / exposed	3 / 30 (10.00%)	9 / 30 (30.00%)	
occurrences (all)	6	17	
Weight increased			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Excoriation			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Fall			

subjects affected / exposed	2 / 30 (6.67%)	1 / 30 (3.33%)	
occurrences (all)	2	1	
Limb injury			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Lumbar vertebral fracture			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Post procedural swelling			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Procedural pain			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	2	
Sunburn			
subjects affected / exposed	0 / 30 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Thermal burn			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Mitral valve incompetence			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Palpitations			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Sinus bradycardia			
subjects affected / exposed	2 / 30 (6.67%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Tachycardia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	

Nervous system disorders			
Amnesia			
subjects affected / exposed	0 / 30 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Asterixis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Ataxia			
subjects affected / exposed	0 / 30 (0.00%)	3 / 30 (10.00%)	
occurrences (all)	0	3	
Cervical radiculopathy			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Coordination abnormal			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	3	
Dizziness			
subjects affected / exposed	5 / 30 (16.67%)	4 / 30 (13.33%)	
occurrences (all)	5	5	
Dysaesthesia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Dysgeusia			
subjects affected / exposed	2 / 30 (6.67%)	3 / 30 (10.00%)	
occurrences (all)	2	3	
Encephalopathy			
subjects affected / exposed	0 / 30 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	6	
Headache			
subjects affected / exposed	4 / 30 (13.33%)	4 / 30 (13.33%)	
occurrences (all)	4	7	
Hepatic encephalopathy			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Hyperaesthesia			

subjects affected / exposed	1 / 30 (3.33%)	1 / 30 (3.33%)	
occurrences (all)	2	1	
Hypoaesthesia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Hypotonia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Lethargy			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Memory impairment			
subjects affected / exposed	1 / 30 (3.33%)	2 / 30 (6.67%)	
occurrences (all)	1	2	
Neuropathy peripheral			
subjects affected / exposed	1 / 30 (3.33%)	6 / 30 (20.00%)	
occurrences (all)	1	8	
Optic neuritis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Orthostatic tremor			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Paraesthesia			
subjects affected / exposed	1 / 30 (3.33%)	3 / 30 (10.00%)	
occurrences (all)	2	3	
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Spinal cord compression			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Tremor			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	1 / 30 (3.33%)	2 / 30 (6.67%)	
occurrences (all)	8	3	
Leukopenia			
subjects affected / exposed	2 / 30 (6.67%)	1 / 30 (3.33%)	
occurrences (all)	2	1	
Neutropenia			
subjects affected / exposed	1 / 30 (3.33%)	1 / 30 (3.33%)	
occurrences (all)	3	1	
Polycythaemia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Thrombocytopenia			
subjects affected / exposed	2 / 30 (6.67%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Ear congestion			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Middle ear inflammation			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Otorrhoea			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Vertigo			
subjects affected / exposed	2 / 30 (6.67%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Vertigo positional			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Eye disorders			

Conjunctival oedema			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Eye discharge			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Eye irritation			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Eye pain			
subjects affected / exposed	1 / 30 (3.33%)	2 / 30 (6.67%)	
occurrences (all)	1	2	
Eye pruritus			
subjects affected / exposed	0 / 30 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Glaucoma			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Lacrimation increased			
subjects affected / exposed	2 / 30 (6.67%)	1 / 30 (3.33%)	
occurrences (all)	2	1	
Ocular hyperaemia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	2	
Periorbital oedema			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Vision blurred			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Visual impairment			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	3	
Gastrointestinal disorders			
Abdominal discomfort			

subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Abdominal distension			
subjects affected / exposed	4 / 30 (13.33%)	2 / 30 (6.67%)	
occurrences (all)	4	2	
Abdominal pain			
subjects affected / exposed	6 / 30 (20.00%)	11 / 30 (36.67%)	
occurrences (all)	8	17	
Abdominal pain lower			
subjects affected / exposed	1 / 30 (3.33%)	3 / 30 (10.00%)	
occurrences (all)	1	3	
Abdominal pain upper			
subjects affected / exposed	5 / 30 (16.67%)	8 / 30 (26.67%)	
occurrences (all)	8	10	
Anal fissure			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Aphthous stomatitis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Ascites			
subjects affected / exposed	4 / 30 (13.33%)	10 / 30 (33.33%)	
occurrences (all)	4	24	
Constipation			
subjects affected / exposed	4 / 30 (13.33%)	11 / 30 (36.67%)	
occurrences (all)	5	16	
Diarrhoea			
subjects affected / exposed	20 / 30 (66.67%)	23 / 30 (76.67%)	
occurrences (all)	38	85	
Dry mouth			
subjects affected / exposed	3 / 30 (10.00%)	4 / 30 (13.33%)	
occurrences (all)	3	4	
Dyspepsia			
subjects affected / exposed	3 / 30 (10.00%)	2 / 30 (6.67%)	
occurrences (all)	4	3	
Dysphagia			

subjects affected / exposed	2 / 30 (6.67%)	1 / 30 (3.33%)	
occurrences (all)	2	1	
Enterocutaneous fistula			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Flatulence			
subjects affected / exposed	2 / 30 (6.67%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Gastritis			
subjects affected / exposed	2 / 30 (6.67%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal pain			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 30 (3.33%)	3 / 30 (10.00%)	
occurrences (all)	1	3	
Gingival bleeding			
subjects affected / exposed	2 / 30 (6.67%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Gingival pain			
subjects affected / exposed	1 / 30 (3.33%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Gingival recession			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Haemorrhoids			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Inguinal hernia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Intestinal obstruction			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Nausea			

subjects affected / exposed	15 / 30 (50.00%)	18 / 30 (60.00%)	
occurrences (all)	18	27	
Odynophagia			
subjects affected / exposed	0 / 30 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Oral pain			
subjects affected / exposed	1 / 30 (3.33%)	1 / 30 (3.33%)	
occurrences (all)	1	2	
Proctalgia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Rectal haemorrhage			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Steatorrhoea			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Stomatitis			
subjects affected / exposed	1 / 30 (3.33%)	2 / 30 (6.67%)	
occurrences (all)	2	2	
Tongue disorder			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Varices oesophageal			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	9 / 30 (30.00%)	12 / 30 (40.00%)	
occurrences (all)	12	18	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Cholecystitis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	

Hepatic failure			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Hepatic pain			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	3	0	
Hyperbilirubinaemia			
subjects affected / exposed	5 / 30 (16.67%)	1 / 30 (3.33%)	
occurrences (all)	6	2	
Jaundice			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Portal hypertension			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Actinic keratosis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Alopecia			
subjects affected / exposed	3 / 30 (10.00%)	5 / 30 (16.67%)	
occurrences (all)	3	6	
Blister			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Decubitus ulcer			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Dry skin			
subjects affected / exposed	4 / 30 (13.33%)	9 / 30 (30.00%)	
occurrences (all)	4	10	
Ecchymosis			

subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)		
occurrences (all)	0	1		
Erythema				
subjects affected / exposed	1 / 30 (3.33%)	5 / 30 (16.67%)		
occurrences (all)	1	5		
Exfoliative rash				
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)		
occurrences (all)	0	1		
Hair texture abnormal				
subjects affected / exposed	1 / 30 (3.33%)	1 / 30 (3.33%)		
occurrences (all)	1	1		
Hyperhidrosis				
subjects affected / exposed	1 / 30 (3.33%)	3 / 30 (10.00%)		
occurrences (all)	2	3		
Night sweats				
subjects affected / exposed	2 / 30 (6.67%)	2 / 30 (6.67%)		
occurrences (all)	2	2		
Pain of skin				
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)		
occurrences (all)	1	0		
Palmar erythema				
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)		
occurrences (all)	0	2		
Palmar-plantar erythrodysaesthesia syndrome				
subjects affected / exposed	11 / 30 (36.67%)	9 / 30 (30.00%)		
occurrences (all)	22	32		
Penile ulceration				
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)		
occurrences (all)	0	1		
Photosensitivity reaction				
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)		
occurrences (all)	1	0		
Pruritus				
subjects affected / exposed	5 / 30 (16.67%)	3 / 30 (10.00%)		
occurrences (all)	5	5		

Pruritus allergic			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Pruritus generalised			
subjects affected / exposed	0 / 30 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Rash			
subjects affected / exposed	9 / 30 (30.00%)	5 / 30 (16.67%)	
occurrences (all)	10	10	
Skin depigmentation			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Skin discolouration			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Skin fissures			
subjects affected / exposed	1 / 30 (3.33%)	1 / 30 (3.33%)	
occurrences (all)	2	1	
Skin lesion			
subjects affected / exposed	1 / 30 (3.33%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Skin reaction			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Skin ulcer			
subjects affected / exposed	1 / 30 (3.33%)	2 / 30 (6.67%)	
occurrences (all)	1	2	
Swelling face			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Urticaria			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Acute kidney injury			

subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Bladder disorder			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Dysuria			
subjects affected / exposed	1 / 30 (3.33%)	2 / 30 (6.67%)	
occurrences (all)	1	3	
Enuresis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Pollakiuria			
subjects affected / exposed	0 / 30 (0.00%)	3 / 30 (10.00%)	
occurrences (all)	0	3	
Proteinuria			
subjects affected / exposed	1 / 30 (3.33%)	3 / 30 (10.00%)	
occurrences (all)	1	5	
Renal failure			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Renal vein thrombosis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Urinary hesitation			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Urinary incontinence			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Urinary retention			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Endocrine disorders			
Hyperparathyroidism			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	

Hypothyroidism			
subjects affected / exposed	2 / 30 (6.67%)	1 / 30 (3.33%)	
occurrences (all)	2	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 30 (20.00%)	8 / 30 (26.67%)	
occurrences (all)	10	13	
Back pain			
subjects affected / exposed	5 / 30 (16.67%)	5 / 30 (16.67%)	
occurrences (all)	6	5	
Bone pain			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Groin pain			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Joint stiffness			
subjects affected / exposed	1 / 30 (3.33%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Muscle spasms			
subjects affected / exposed	3 / 30 (10.00%)	4 / 30 (13.33%)	
occurrences (all)	3	5	
Muscle tightness			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Muscular weakness			
subjects affected / exposed	2 / 30 (6.67%)	1 / 30 (3.33%)	
occurrences (all)	2	1	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal pain			
subjects affected / exposed	2 / 30 (6.67%)	4 / 30 (13.33%)	
occurrences (all)	3	5	
Myalgia			

subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Neck pain			
subjects affected / exposed	2 / 30 (6.67%)	3 / 30 (10.00%)	
occurrences (all)	2	3	
Pain in extremity			
subjects affected / exposed	3 / 30 (10.00%)	5 / 30 (16.67%)	
occurrences (all)	3	8	
Pain in jaw			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	2	
Spinal pain			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 30 (3.33%)	2 / 30 (6.67%)	
occurrences (all)	1	2	
Candida infection			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Cellulitis			
subjects affected / exposed	1 / 30 (3.33%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Clostridium difficile colitis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Device related infection			
subjects affected / exposed	1 / 30 (3.33%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Ear lobe infection			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Folliculitis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	3	

Gastroenteritis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	3	
Genital candidiasis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Gingivitis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Groin abscess			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Herpes virus infection			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Infection			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Localised infection			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Lung infection			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	1 / 30 (3.33%)	4 / 30 (13.33%)	
occurrences (all)	2	4	
Oesophageal candidiasis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	2	
Oral candidiasis			
subjects affected / exposed	1 / 30 (3.33%)	2 / 30 (6.67%)	
occurrences (all)	2	2	

Otitis media			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Postoperative wound infection			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Rhinitis			
subjects affected / exposed	0 / 30 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Sinusitis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Skin candida			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Staphylococcal infection			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	0 / 30 (0.00%)	3 / 30 (10.00%)	
occurrences (all)	0	3	
Urinary tract infection			
subjects affected / exposed	2 / 30 (6.67%)	2 / 30 (6.67%)	
occurrences (all)	2	3	
Viral infection			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Cachexia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Decreased appetite			

subjects affected / exposed	9 / 30 (30.00%)	16 / 30 (53.33%)	
occurrences (all)	12	22	
Dehydration			
subjects affected / exposed	2 / 30 (6.67%)	5 / 30 (16.67%)	
occurrences (all)	2	5	
Failure to thrive			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Hypercalcaemia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Hyperglycaemia			
subjects affected / exposed	1 / 30 (3.33%)	1 / 30 (3.33%)	
occurrences (all)	1	2	
Hyperkalaemia			
subjects affected / exposed	2 / 30 (6.67%)	2 / 30 (6.67%)	
occurrences (all)	3	2	
Hyperuricaemia			
subjects affected / exposed	2 / 30 (6.67%)	1 / 30 (3.33%)	
occurrences (all)	3	1	
Hypocalcaemia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Hypoglycaemia			
subjects affected / exposed	1 / 30 (3.33%)	1 / 30 (3.33%)	
occurrences (all)	1	2	
Hypokalaemia			
subjects affected / exposed	2 / 30 (6.67%)	4 / 30 (13.33%)	
occurrences (all)	2	5	
Hypomagnesaemia			
subjects affected / exposed	4 / 30 (13.33%)	1 / 30 (3.33%)	
occurrences (all)	5	1	
Hyponatraemia			
subjects affected / exposed	2 / 30 (6.67%)	1 / 30 (3.33%)	
occurrences (all)	3	2	
Hypophosphataemia			

subjects affected / exposed	3 / 30 (10.00%)	1 / 30 (3.33%)	
occurrences (all)	5	1	
Malnutrition			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 December 2009	- Introduced a new cohort (B) (trebananib 15 mg/kg IV QW plus sorafenib 400 mg PO BID) with a planned enrollment of approximately 30 additional subjects - Extended the enrollment period to 15 months to facilitate the enrollment of the additional 30 subjects - Updated in the introduction the clinical immunogenicity data across the phase 1 trebananib program - Provided clarification regarding inclusion/exclusion criteria for consistency across the trebananib program - Provided clarification and better defined the clinical hypothesis of the study - Added thyroid function test as a required laboratory test to monitor incidence of hypothyroidism associated with tyrosine kinase inhibitors - Provided guidance regarding trebananib dosing in case of adverse event of hypertension, edema/lymphedema, and infusion reactions - Added trebananib toxicity management sections (edema/lymphedema, hypertension, infusion reactions) - Removed all specific and detailed information related to packaging and formulation of trebananib and matching placebo, and consolidated details in a pharmacy binder, which was sent to investigators with the protocol (to ensure sites always had the most accurate information). - Clarified the definition of the primary endpoint as time to progression rate at 18 weeks
01 March 2011	- Changed the primary endpoint to progression-free survival at 4 months; revised sample size section - Added an additional safety review for cohort A (after 20 subjects) - Provided an update regarding the toxicity management guidance for the adverse events of edema/lymphedema, hypertension, and hypokalemia
18 July 2011	- Added new section for the toxicity management of trebananib related pleural effusion and ascites - Decreased the radiologic scanning frequency interval after 2 years on study - Corrected the INR value for inclusion criteria to INR ≤ 2.2 per Child-Pugh Classification - Added guidelines for proscribed medications including immune modulators and strong CYP3A4 inducers during the study - Added the new pregnancy reporting section and form

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported