Clinical trial results:
A Multicenter, Randomized, Open-Label, Phase 3 Trial to Compare the Efficacy and Safety of Lenvatinib (E7080) Versus Sorafenib in First-Line Treatment of Subjects With Unresectable Hepatocellular Carcinoma

Summary

EudraCT number	2012-002992-33
Trial protocol	IT DE GB ES PL BE
Global end of trial date	10 March 2021

Results information

Result version number	v2 (current)
This version publication date	24 March 2022
First version publication date	12 September 2018
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	E7080-G000-304

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01761266
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Eisai, Inc.
Sponsor organisation address	155 Tice Boulevard, Woodcliff Lake, New Jersey, United States, 07677
Public contact	Eisai Medical Information, Eisai Inc., +1 888-274-2378, esi_oncmedinfo@eisai.com
Scientific contact	Eisai Medical Information, Eisai, Inc., +1 888-274-2378, esi_oncmedinfo@eisai.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	10 March 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 March 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to compare overall survival (OS) in subjects treated with lenvatinib versus sorafenib as a first-line treatment in subjects with unresectable heptocellular carcinoma (HCC).

Protection of trial subjects:

This study was conducted in accordance with standard operating procedures (SOPs) of the sponsor (or designee), which are designed to ensure adherence to Good Clinical Practice (GCP) guidelines as required by the following: - Principles of the World Medical Association Declaration of Helsinki (World Medical Association, 2008) - International Council on Harmonisation (ICH) E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use - Title 21 of the United States (US) Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and Institutional Review Board (IRB) regulations and applicable sections of US 21 CFR Part 312 - European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any European Union (EU) country. All suspected unexpected serious adverse reactions were reported, as required, to the Competent Authorities of all involved EU member states. - Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan’s GCP Subject Information and Informed Consent.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 March 2013
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	China: 213
Country: Number of subjects enrolled	Hong Kong: 21
Country: Number of subjects enrolled	Japan: 168
Country: Number of subjects enrolled	Korea, Republic of: 142
Country: Number of subjects enrolled	Malaysia: 11
Country: Number of subjects enrolled	Philippines: 7
Country: Number of subjects enrolled	Singapore: 16
Country: Number of subjects enrolled	Taiwan: 54
Country: Number of subjects enrolled	Thailand: 8
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Canada: 1

Country: Number of subjects enrolled	France: 52
Country: Number of subjects enrolled	Germany: 20
Country: Number of subjects enrolled	Israel: 3
Country: Number of subjects enrolled	Italy: 28
Country: Number of subjects enrolled	Poland: 35
Country: Number of subjects enrolled	Russian Federation: 73
Country: Number of subjects enrolled	Spain: 15
Country: Number of subjects enrolled	United Kingdom: 20
Country: Number of subjects enrolled	United States: 63
Worldwide total number of subjects	954
EEA total number of subjects	154

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)	553
From 65 to 84 years	397
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study at 154 investigative sites in Australia, Belgium, Canada, China, France, Germany, Hong Kong, Israel, Italy, Japan, South Korea, Malaysia, Philippines, Poland, Russia, Singapore, Spain, Taiwan, Thailand, United Kingdom, and the United States from 1 March 2013 to 10 March 2021.

Pre-assignment

Screening details:

A total of 1,492 subjects were screened, 954 subjects were enrolled and randomized, out of which 951 subjects were treated in the study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Lenvatinib

Arm description:

Subjects received lenvatinib capsules 12 milligram (mg) based on the subject's body weight greater than or equal to (>=) 60 kilogram (kg) or 8 mg based on the subject's body weight less than (<) 60 kg at baseline, orally, once daily (QD) in continuous 28-day treatment cycles up to documented disease progression, development of unacceptable toxicity, subject request, or withdrawal of consent.

Arm type	Experimental
Investigational medicinal product name	Lenvatinib
Investigational medicinal product code	E7080
Other name	Lenvima
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Lenvatinib capsule 12 mg based on the subject's body weight >=60 kg or 8 mg based on the subject's body weight <60 kg at baseline, orally, QD in continuous 28-day treatment cycles up to documented disease progression, development of unacceptable toxicity, subject request, or withdrawal of consent.

Arm title	Sorafenib

Arm description:

Subjects received sorafenib 400 mg tablets, orally, twice daily (BID) in continuous 28-day treatment cycles up to documented disease progression, development of unacceptable toxicity, subject request, or withdrawal of consent.

Arm type	Experimental
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 400 mg tablets, orally, BID in continuous 28-day treatment cycles up to documented disease progression, development of unacceptable toxicity, subject request, or withdrawal of consent.

Number of subjects in period 1	Lenvatinib	Sorafenib
Started	478	476
Treated	476	475
Completed	0	0
Not completed	478	476
Consent withdrawn by subject	14	10
Death	415	402
Sponsor Decision	41	52
Lost to follow-up	8	12

Baseline characteristics

Reporting groups	
Reporting group title	Lenvatinib
Reporting group description:	
Subjects received lenvatinib capsules 12 milligram (mg) based on the subject's body weight greater than or equal to (>=) 60 kilogram (kg) or 8 mg based on the subject's body weight less than (<) 60 kg at baseline, orally, once daily (QD) in continuous 28-day treatment cycles up to documented disease progression, development of unacceptable toxicity, subject request, or withdrawal of consent.	
Reporting group title	Sorafenib
Reporting group description:	
Subjects received sorafenib 400 mg tablets, orally, twice daily (BID) in continuous 28-day treatment cycles up to documented disease progression, development of unacceptable toxicity, subject request, or withdrawal of consent.	

Reporting group values	Lenvatinib	Sorafenib	Total
Number of subjects	478	476	954
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	61.3	61.2	
standard deviation	± 11.69	± 12.01	-
Sex: Female, Male Units: subjects			
Female	73	75	148
Male	405	401	806
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	6	11	17
Not Hispanic or Latino	472	465	937
Unknown or Not Reported	0	0	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	0	1
Asian	334	326	660
Native Hawaiian or Other Pacific Islander	0	1	1
Black or African American	7	6	13
White	135	141	276
Other	1	2	3

End points

End points reporting groups

Reporting group title	Lenvatinib

Reporting group description:

Subjects received lenvatinib capsules 12 milligram (mg) based on the subject's body weight greater than or equal to (>=) 60 kilogram (kg) or 8 mg based on the subject's body weight less than (<) 60 kg at baseline, orally, once daily (QD) in continuous 28-day treatment cycles up to documented disease progression, development of unacceptable toxicity, subject request, or withdrawal of consent.

Reporting group title	Sorafenib

Reporting group description:

Subjects received sorafenib 400 mg tablets, orally, twice daily (BID) in continuous 28-day treatment cycles up to documented disease progression, development of unacceptable toxicity, subject request, or withdrawal of consent.

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)[1]

End point description:

OS was defined as the duration from the date of randomization until the date of death from any cause. Subjects who were lost to follow-up were censored at the last date the subject was known to be alive, and subjects who remained alive were censored at the time of data cutoff. The full analysis set (FAS) included all subjects who were randomized.

End point type	Primary

End point timeframe:

From date of randomization until date of death from any cause (approximately up to 3.8 years)

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 statistical analysis was planned for this endpoint.

End point values	Lenvatinib	Sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	478	476		
Units: months				
median (confidence interval 95%)	13.6 (12.1 to 14.9)	12.3 (10.4 to 13.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

PFS was defined as the time from the date of randomization to the date of first documentation of disease progression based on modified Response Evaluation Criteria in Solid Tumors (mRECIST), or date of death, whichever occurred first. Disease progression was defined as at least a 20 percent (%) increase in the sum of diameters of target lesions, taking as reference the baseline sum of diameters of target lesions. As planned, data for this secondary endpoint was collected and analyzed up to the primary completion date. The FAS included all subjects who were randomized.

End point type	Secondary

End point timeframe:

From the date of randomization to the date of first documentation of disease progression, or date of death, whichever occurred first (approximately up to 3.8 years)

End point values	Lenvatinib	Sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	478	476		
Units: months				
median (confidence interval 95%)	7.4 (6.9 to 8.8)	3.7 (3.6 to 4.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression (TTP)

End point title	Time to Progression (TTP)

End point description:

TTP was defined as the time from the date of randomization to the date of first documentation of disease progression based on mRECIST. Disease progression was defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the baseline sum of diameters of target lesions. As planned, data for this secondary endpoint was collected and analyzed up to the primary completion date. The FAS included all subjects who were randomized.

End point type	Secondary

End point timeframe:

The time from the date of randomization to the date of first documentation of disease progression (approximately up to 3.8 years)

End point values	Lenvatinib	Sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	478	476		
Units: months				
median (confidence interval 95%)	8.9 (7.4 to 9.2)	3.7 (3.6 to 5.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:

ORR was defined as the percentage of subjects with a best overall response of complete response (CR)

or partial response (PR) based on mRECIST. CR was defined as disappearance of any intratumoral arterial enhancement in all target lesions. PR was defined as at least a 30% decrease in the sum of diameters of viable (enhancement of arterial phase) target lesions taking as reference to the baseline sum of the diameters of target lesions. As planned, data for this secondary endpoint was collected and analyzed up to the primary completion date. The FAS included all subjects who were randomized.

End point type	Secondary

End point timeframe:

From the date of randomization to the date of first documentation of disease progression, or date of death, whichever occurred first (approximately up to 3.8 years)

End point values	Lenvatinib	Sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	478	476		
Units: percentage of subjects				
number (confidence interval 95%)	24.1 (20.2 to 27.9)	9.2 (6.6 to 11.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Clinically Meaningful Worsening of Health Related Quality of Life (HRQoL) Assessed Using European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)

End point title	Time to Clinically Meaningful Worsening of Health Related Quality of Life (HRQoL) Assessed Using European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)

End point description:

EORTC QLQ-C30 included 30 questions comprising 9 multi-item scales: 5 functional scales (physical, role, cognitive, emotional, and social) and 9 symptom scales (fatigue, pain, nausea/vomiting, dyspnoea, appetite loss, insomnia, constipation, diarrhea and financial difficulties) and a single global health and QOL status score. Most questions used a 4-point scale (1=Not at all to 4=Very much); 2 questions used a 7-point scale (1= Very poor to 7=Excellent). All domain scores were calculated as an average of item scores and transformed to 0 to 100 score range. A high score for a functional scale represents a high/healthy level of functioning, a high score for the global health status/quality of life (QoL) represents a high QoL, but a high score for a symptom scale/item represents a high level of symptomatology/problem. As planned, data for this secondary endpoint was collected and analyzed up to the primary completion date. The FAS included all subjects who were randomized.

End point type	Secondary

End point timeframe:

Baseline up to Off-Treatment Visit (approximately up to 3.8 years)

End point values	Lenvatinib	Sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	478	476		
Units: months				
median (confidence interval 95%)	1.7 (1.05 to 1.84)	1.8 (1.05 to 1.84)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Clinically Meaningful Worsening of HRQoL Assessed Using - EORTC QLQ- Hepatocellular Carcinoma Domain (HCC 18)

End point title	Time to Clinically Meaningful Worsening of HRQoL Assessed Using - EORTC QLQ- Hepatocellular Carcinoma Domain (HCC 18)

End point description:

The EORTC QLQ-HCC-18 was an 18-item questionnaire design used along with the 30-item EORTC QLQ-C30. EORTC QLQ-HCC 18 questionnaire included 8 symptom scales such as fatigue, jaundice, body image, nutrition, pain, fever, sex life and abdominal swelling. Each individual item ranges from 1 to 4, where 1 = "not at all" and 4 = "very much." All domain scores were calculated as an average of item scores and transformed to 0 to 100 score range. A high score for a functional scale represented a high/healthy level of functioning, a high score for the global health status/quality of life (QoL) represented a high QoL, but a high score for a symptom scale/item represented a high level of symptomatology/problem. As planned, data for this secondary endpoint was collected and analyzed up to the primary completion date. The FAS included all subjects who were randomized.

End point type	Secondary

End point timeframe:

Baseline up to Off-Treatment Visit (approximately up to 3.8 years)

End point values	Lenvatinib	Sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	478	476		
Units: months				
median (confidence interval 95%)				
Fatigue	1.9 (1.81 to 1.97)	1.8 (1.74 to 1.87)		
Jaundice	4.6 (3.72 to 5.52)	3.7 (2.86 to 4.73)		
Body Image	2.8 (2.73 to 3.68)	1.9 (1.84 to 2.73)		
Nutrition	4.1 (3.68 to 5.52)	2.8 (2.04 to 3.06)		
Pain	2.7 (1.97 to 2.83)	2.8 (2.73 to 3.72)		
Fever	5.5 (4.57 to 6.51)	3.7 (2.99 to 5.52)		
Sex Life	7.4 (5.46 to 9.17)	6.7 (4.60 to 13.78)		
Abdominal swelling	7.4 (5.52 to 9.24)	7.4 (5.46 to 10.13)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Clinically Meaningful Worsening of HRQoL Assessed Using EuroQol Five Dimension Health Questionnaire (EQ-5D-3L)

End point title	Time to Clinically Meaningful Worsening of HRQoL Assessed Using EuroQol Five Dimension Health Questionnaire (EQ-5D-3L)

End point description:

The EuroQol five dimension health questionnaire (EQ-5D-3L) assesses quality of life along 5 dimensions. Subjects rate 5 aspects of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) by choosing from 3 answering options (1=no problems; 2=some problems; 3=extreme problems). The summed score ranges from 3-15 with "3" corresponding to no problems; "15" corresponding to severe problems in 5 dimensions. EQ-5D-3L also included EQ visual analogue scale (VAS) that ranges between 100 (best imaginable health); 0 (worst imaginable health). Decrease from baseline in EQ-5D-3L signifies improvement. Total index EQ-5D-3L summary score weighted with range -0.594 (worst) to 1.0 (best). EQ-5D-3L also included EQ health utilities index (HUI) where 1.00 indicated perfect health while score of 0.00 indicated death. As planned, data for this secondary endpoint was collected and analyzed up to the primary completion date.The FAS included all subjects who were randomized.

End point type	Secondary

End point timeframe:

Baseline up to Off-Treatment Visit (approximately up to 3.8 years)

End point values	Lenvatinib	Sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	478	476		
Units: months				
median (confidence interval 95%)				
VAS	2.8 (2.17 to 3.65)	1.9 (1.84 to 2.33)		
HUI	2.8 (1.97 to 3.52)	1.9 (1.84 to 2.66)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Drug Concentration-time Curve (AUC) for Lenvatinib

End point title	Area Under the Plasma Drug Concentration-time Curve (AUC) for Lenvatinib

End point description:

AUC was assessed on Cycle 1 Day 1, Cycle 2 Day 1 and Cycle 1 Day 15. Summarized data for all time points was reported. As planned, data for this secondary endpoint was collected and analyzed up to the primary completion date. The pharmacokinetic (PK) analysis set included all subjects who had received at least 1 dose of lenvatinib and had at least 1 quantifiable lenvatinib concentration.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1, Cycle 2 Day 1: pre-dose, 0.5-4 and 6-10 hours post-dose; Cycle 1 Day 15: pre-dose, 2-12 hours post-dose (cycle length= 28 days)

End point values	Lenvatinib	Sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	150	318		
Units: nanogram*hour per milliliter (ng*h/mL)				
arithmetic mean (standard deviation)	1969.6 (± 743.0)	2120.9 (± 685.6)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Disease control rate (DCR)

End point title	Disease control rate (DCR)

End point description:

DCR was defined as the percentage of subjects with a best overall response of CR or PR, or stable disease (SD). Best overall response of SD must have been >=7 weeks after randomization. CR was defined as disappearance of any intratumoral arterial enhancement in all target lesions. PR was defined as at least a 30% decrease in the sum of diameters of viable (enhancement of arterial phase) target lesions taking as reference the baseline sum of the diameters of target lesions. SD was when a case does not qualify for either PR or PD and was new non-target lesions. PD was defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the baseline sum of diameters of target lesions. As planned, data for this pre-specified endpoint was collected and analyzed up to the primary completion date. The FAS included all subjects who were randomized.

End point type	Other pre-specified

End point timeframe:

From the date of randomization to the date of first documentation of disease progression, or date of death, whichever occurred first (approximately up to 3.8 years)

End point values	Lenvatinib	Sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	478	476		
Units: percentage of subjects				
number (confidence interval 95%)	75.5 (71.7 to 79.4)	60.5 (56.1 to 64.9)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Clinical Benefit Rate (CBR)

End point title	Clinical Benefit Rate (CBR)

End point description:

CBR was defined as percentage of subjects with best overall response of CR or PR or durable SD (duration of SD >=23 weeks after randomization). For subjects whose best overall response (BOR) was SD, duration of SD was defined as time from date of randomization to first documented PD or death, whichever occurred first. CR was defined as disappearance of any intratumoral arterial enhancement in all target lesions. PR was defined as at least a 30% decrease in the sum of diameters of viable (enhancement of arterial phase) target lesions taking as reference baseline sum of diameters of target lesions. SD was when a case does not qualify for either PR or PD. PD was defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the baseline sum of diameters of target lesions. As planned, data for this pre-specified endpoint was collected and analyzed up to the primary completion date. The FAS included all subjects who were randomized.

End point type	Other pre-specified

End point timeframe:

From the date of randomization to the date of first documentation of disease progression, or date of death, whichever occurred first (approximately up to 3.8 years)

End point values	Lenvatinib	Sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	478	476		
Units: percentage of subjects				
number (confidence interval 95%)	59.0 (54.6 to 63.4)	38.4 (34.1 to 42.8)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percent Change from Baseline in Serum Biomarker

End point title	Percent Change from Baseline in Serum Biomarker

End point description:

The serum biomarkers analysed were angiopoietin-2 (ANG2), fibroblast growth factor 19 (FGF19), fibroblast growth factor 21 (FGF21), fibroblast growth factor 23 (FGF23) and vascular endothelial growth factor (VEGF) as blood serum biomarkers, and protein induced by vitamin K absence or antagonist-II (PIVKA-II) as a blood tumor marker in serum. As planned, data for this pre-specified endpoint was collected and analyzed up to the primary completion date. The pharmacodynamics (PD) analysis set included all subjects who received at least 1 dose of study drug and had evaluable PD data. Here "n" was subjects who were evaluable for the outcome measure at given time points.

End point type	Other pre-specified

End point timeframe:

Cycle 1 Day 15, Cycle 2 Day 1, Cycle 3 Day 1, Cycle 4 Day 1, Cycle 5 Day 1, Cycle 6 Day 1, Cycle 7 Day 1, Cycle 8 Day 1, Cycle 9 Day 1 and at the Off-Treatment Visit (approximately up to 3.8 years)

End point values	Lenvatinib	Sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	48		
Units: percent change				
median (standard deviation)				
ANG 2: Cycle 1 Day 15	-28.1 (± 15.94)	8.9 (± 23.96)		
ANG 2: Cycle 2 Day 1	-28.8 (± 16.53)	-0.9 (± 24.06)		
ANG 2: Cycle 3 Day 1	-32.2 (± 23.23)	0.5 (± 26.62)		
ANG 2: Cycle 4 Day 1	-35.6 (± 22.91)	-4.5 (± 20.05)		
ANG 2: Cycle 5 Day 1	-38.9 (± 19.83)	7.0 (± 23.25)		
ANG 2: Cycle 6 Day 1	-36.7 (± 23.59)	-3.6 (± 24.82)		
ANG 2: Cycle 7 Day 1	-41.4 (± 21.20)	1.0 (± 32.83)		
ANG 2: Cycle 8 Day 1	-40.2 (± 25.33)	-6.7 (± 31.26)		
ANG 2: Cycle 9 Day 1	-39.6 (± 14.04)	-1.1 (± 29.68)		
ANG 2: Off-Treatment	11.7 (± 99.13)	16.8 (± 27.88)		
FGF19: Cycle 1 Day 15	75.0 (± 155.01)	1.3 (± 83.65)		
FGF19: Cycle 2 Day 1	66.5 (± 134.26)	36.6 (± 119.65)		
FGF19: Cycle 3 Day 1	86.9 (± 123.85)	22.8 (± 70.58)		
FGF19: Cycle 4 Day 1	208.1 (± 602.11)	46.8 (± 214.14)		
FGF19: Cycle 5 Day 1	152.8 (± 228.37)	-1.0 (± 40.36)		
FGF19: Cycle 6 Day 1	119.8 (± 203.81)	26.9 (± 67.13)		
FGF19: Cycle 7 Day 1	64.4 (± 101.97)	-5.9 (± 57.39)		
FGF19: Cycle 8 Day 1	95.8 (± 135.31)	53.9 (± 113.79)		
FGF19: Cycle 9 Day 1	159.3 (± 202.00)	56.6 (± 109.46)		
FGF19: Off-Treatment	140.1 (± 270.73)	9.0 (± 64.17)		
FGF 21: Cycle 1 Day 15	22.0 (± 75.22)	4.0 (± 43.14)		
FGF 21: Cycle 2 Day 1	15.7 (± 77.44)	18.6 (± 57.18)		
FGF 21: Cycle 3 Day 1	38.3 (± 38.3)	49.4 (± 76.43)		
FGF 21: Cycle 4 Day 1	42.9 (± 145.43)	32.8 (± 70.63)		
FGF 21: Cycle 5 Day 1	41.0 (± 95.97)	31.1 (± 43.15)		
FGF 21: Cycle 6 Day 1	52.6 (± 168.22)	23.2 (± 40.90)		

FGF 21: Cycle 7 Day 1	63.4 (± 128.34)	23.7 (± 53.84)		
FGF 21 : Cycle 8 Day1	38.3 (± 115.53)	17.0 (± 68.51)		
FGF 21: Cycle 9 Day1	59.1 (± 108.39)	68.9 (± 103.55)		
FGF 21: Off-Treatment	141.4 (± 340.51)	104.9 (± 183.28)		
FGF 23: Cycle 1 Day15	23.9 (± 49.01)	-16.3 (± 36.14)		
FGF 23: Cycle 2 Day 1	20.9 (± 56.91)	-6.2 (± 48.18)		
FGF 23: Cycle 3 Day 1	25.5 (± 45.27)	17.3 (± 75.25)		
FGF 23: Cycle 4 Day 1	29.5 (± 48.38)	14.2 (± 49.29)		
FGF 23: Cycle 5 Day 1	29.6 (± 63.69)	1.0 (± 47.28)		
FGF 23: Cycle 6 Day 1	26.3 (± 54.57)	-10.6 (± 46.15)		
FGF 23: Cycle 7 Day 1	31.5 (± 57.44)	0.7 (± 46.95)		
FGF 23: Cycle 8 Day 1	38.1 (± 67.35)	2.8 (± 43.84)		
FGF 23: Cycle 9 Day 1	23.2 (± 62.58)	0.5 (± 38.74)		
FGF 23: Off-Treatment	17.8 (± 73.59)	14.2 (± 47.11)		
PIVKA-II: Cycle 1 Day 15	80.0 (± 171.41)	166.9 (± 256.04)		
PIVKA-II: Cycle 2 Day 1	169.7 (± 329.33)	243.8 (± 416.82)		
PIVKA-II: Cycle 3 Day 1	252.4 (± 611.40)	218.7 (± 281.45)		
PIVKA-II: Cycle 4 Day 1	371.7 (± 812.45)	196.2 (± 348.80)		
PIVKA-II: Cycle 5 Day 1	628.2 (± 1752.64)	369.5 (± 766.59)		
PIVKA-II: Cycle 6 Day 1	648.7 (± 2746.41)	415.7 (± 554.27)		
PIVKA-II: Cycle 7 Day 1	184.8 (± 352.75)	703.6 (± 1226.58)		
PIVKA-II: Cycle 8 Day 1	277.8 (± 481.53)	724.0 (± 1257.87)		
PIVKA-II: Cycle 9 Day 1	318.8 (± 577.21)	859.1 (± 1492.93)		
PIVKA-II: Off-Treatment	809.3 (± 1827.42)	272.5 (± 489.60)		
VEGF: Cycle 1 Day 15	157.5 (± 300.21)	97.4 (± 118.43)		
VEGF: Cycle 2 Day 1	128.9 (± 333.85)	94.0 (± 180.80)		
VEGF: Cycle 3 Day 1	97.7 (± 162.39)	66.0 (± 124.58)		
VEGF: Cycle 4 Day 1	113.4 (± 231.19)	76.1 (± 111.20)		
VEGF: Cycle 5 Day 1	132.4 (± 249.59)	116.2 (± 215.57)		
VEGF: Cycle 6 Day 1	113.1 (± 219.36)	130.9 (± 341.12)		
VEGF: Cycle 7 Day 1	133.1 (± 383.43)	96.9 (± 173.77)		
VEGF: Cycle 8 Day 1	148.7 (± 349.58)	181.1 (± 399.67)		
VEGF: Cycle 9 Day 1	129.6 (± 215.05)	135.6 (± 267.61)		
VEGF: Off-Treatment	127.1 (± 266.64)	147.8 (± 304.31)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All treatment-emergent adverse events were collected from first dose of study drug (Baseline) up to 30 days after last dose of study drug (approximately up to 8 years)

Adverse event reporting additional description:

The safety analysis set included all subjects who received at least 1 dose of study drug. Total number of Deaths (all-causes) was reported for all subjects randomized that is Total number of subjects exposed for Lenvatinib were 478 and for Sorafenib were 476.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Sorafenib

Reporting group description:

Subjects received sorafenib 400 mg tablets, orally, twice daily in continuous 28-day treatment cycles up to documented disease progression, development of unacceptable toxicity, subject request, or withdrawal of consent.

Reporting group title	Lenvatinib

Reporting group description:

Subjects received lenvatinib capsules 12 mg based on the subject's body weight >=60 kg or 8 mg based on the subject's body weight <60 kg at baseline, orally, once daily (QD) in continuous 28-day treatment cycles up to documented disease progression, development of unacceptable toxicity, subject request, or withdrawal of consent.

Serious adverse events	Sorafenib	Lenvatinib	
Total subjects affected by serious adverse events			
subjects affected / exposed	149 / 475 (31.37%)	209 / 476 (43.91%)	
number of deaths (all causes)	402	415	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	14 / 475 (2.95%)	11 / 476 (2.31%)	
occurrences causally related to treatment / all	0 / 14	0 / 12	
deaths causally related to treatment / all	0 / 14	0 / 11	
Cancer pain			
subjects affected / exposed	0 / 475 (0.00%)	4 / 476 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			

subjects affected / exposed	3 / 475 (0.63%)	3 / 476 (0.63%)	
occurrences causally related to treatment / all	2 / 4	1 / 4	
deaths causally related to treatment / all	0 / 1	0 / 1	
Liver carcinoma ruptured			
subjects affected / exposed	1 / 475 (0.21%)	2 / 476 (0.42%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Metastases to central nervous system			
subjects affected / exposed	0 / 475 (0.00%)	2 / 476 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastases to spine			
subjects affected / exposed	1 / 475 (0.21%)	2 / 476 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected neoplasm			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial tumour haemorrhage			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningioma			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bone			
subjects affected / exposed	2 / 475 (0.42%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma			

subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour necrosis			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	2 / 475 (0.42%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour rupture			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	1 / 475 (0.21%)	0 / 476 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant ascites			
subjects affected / exposed	1 / 475 (0.21%)	0 / 476 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant pleural effusion			
subjects affected / exposed	1 / 475 (0.21%)	0 / 476 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasma cell myeloma			
subjects affected / exposed	1 / 475 (0.21%)	0 / 476 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mantle cell lymphoma			

subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to adrenals			
subjects affected / exposed	1 / 475 (0.21%)	0 / 476 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic dissection			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Deep vein thrombosis			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock			
subjects affected / exposed	1 / 475 (0.21%)	0 / 476 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 475 (0.21%)	0 / 476 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis superficial			

subjects affected / exposed	1 / 475 (0.21%)	0 / 476 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	5 / 475 (1.05%)	7 / 476 (1.47%)	
occurrences causally related to treatment / all	4 / 6	4 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	1 / 475 (0.21%)	7 / 476 (1.47%)	
occurrences causally related to treatment / all	0 / 1	4 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	3 / 475 (0.63%)	5 / 476 (1.05%)	
occurrences causally related to treatment / all	0 / 4	1 / 5	
deaths causally related to treatment / all	0 / 1	0 / 2	
Oedema peripheral			
subjects affected / exposed	1 / 475 (0.21%)	3 / 476 (0.63%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	2 / 475 (0.42%)	2 / 476 (0.42%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 475 (0.21%)	2 / 476 (0.42%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Death			
subjects affected / exposed	0 / 475 (0.00%)	2 / 476 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Generalised oedema			

subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral swelling			
subjects affected / exposed	1 / 475 (0.21%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Organ failure			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sudden death			
subjects affected / exposed	2 / 475 (0.42%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	1 / 2	0 / 1	
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 475 (0.00%)	2 / 476 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 475 (0.42%)	5 / 476 (1.05%)	
occurrences causally related to treatment / all	0 / 2	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary embolism			
subjects affected / exposed	2 / 475 (0.42%)	4 / 476 (0.84%)	
occurrences causally related to treatment / all	1 / 2	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia aspiration			
subjects affected / exposed	0 / 475 (0.00%)	3 / 476 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 2	

Respiratory failure			
subjects affected / exposed	3 / 475 (0.63%)	3 / 476 (0.63%)	
occurrences causally related to treatment / all	1 / 3	3 / 4	
deaths causally related to treatment / all	1 / 3	2 / 3	
Hepatopulmonary syndrome			
subjects affected / exposed	0 / 475 (0.00%)	2 / 476 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 475 (0.21%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Hiccups			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising bronchiolitis			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiogenic pulmonary oedema			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oropharyngeal pain			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary infarction			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumothorax			

subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
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	2 / 475 (0.42%)	0 / 476 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 475 (0.21%)	0 / 476 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Major depression			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	2 / 475 (0.42%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood bilirubin increased			
subjects affected / exposed	1 / 475 (0.21%)	7 / 476 (1.47%)	
occurrences causally related to treatment / all	1 / 1	3 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase			

increased			
subjects affected / exposed	1 / 475 (0.21%)	2 / 476 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood pressure decreased			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium test positive			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
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 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	2 / 475 (0.42%)	0 / 476 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			

subjects affected / exposed	2 / 475 (0.42%)	0 / 476 (0.00%)	
occurrences causally related to treatment / all	5 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 475 (0.00%)	2 / 476 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intentional overdose			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foreign body			
subjects affected / exposed	1 / 475 (0.21%)	0 / 476 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax traumatic			
subjects affected / exposed	1 / 475 (0.21%)	0 / 476 (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	2 / 475 (0.42%)	0 / 476 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 475 (0.21%)	0 / 476 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Traumatic haematoma			
subjects affected / exposed	1 / 475 (0.21%)	0 / 476 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 475 (0.21%)	4 / 476 (0.84%)	
occurrences causally related to treatment / all	0 / 1	4 / 5	
deaths causally related to treatment / all	0 / 0	1 / 1	
Atrial fibrillation			
subjects affected / exposed	1 / 475 (0.21%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	0 / 475 (0.00%)	2 / 476 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Acute myocardial infarction			
subjects affected / exposed	1 / 475 (0.21%)	0 / 476 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 475 (0.21%)	0 / 476 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart valve stenosis			

subjects affected / exposed	1 / 475 (0.21%)	0 / 476 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 475 (0.21%)	0 / 476 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Nervous system disorders			
Hepatic encephalopathy			
subjects affected / exposed	3 / 475 (0.63%)	21 / 476 (4.41%)	
occurrences causally related to treatment / all	1 / 4	13 / 35	
deaths causally related to treatment / all	0 / 0	0 / 2	
Cerebral haemorrhage			
subjects affected / exposed	0 / 475 (0.00%)	3 / 476 (0.63%)	
occurrences causally related to treatment / all	0 / 0	5 / 5	
deaths causally related to treatment / all	0 / 0	3 / 3	
Coma hepatic			
subjects affected / exposed	1 / 475 (0.21%)	3 / 476 (0.63%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 2	
Cerebral infarction			
subjects affected / exposed	0 / 475 (0.00%)	2 / 476 (0.42%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 475 (0.21%)	2 / 476 (0.42%)	
occurrences causally related to treatment / all	1 / 1	2 / 4	
deaths causally related to treatment / all	0 / 0	1 / 2	
Headache			

subjects affected / exposed	0 / 475 (0.00%)	2 / 476 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 475 (0.21%)	2 / 476 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	0 / 475 (0.00%)	2 / 476 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diplegia			
subjects affected / exposed	1 / 475 (0.21%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disturbance in attention			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paralysis			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paralysis recurrent laryngeal nerve			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Posterior reversible encephalopathy syndrome			

subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal ganglia haemorrhage			
subjects affected / exposed	1 / 475 (0.21%)	0 / 476 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	1 / 475 (0.21%)	0 / 476 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 475 (0.21%)	0 / 476 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Loss of consciousness			
subjects affected / exposed	1 / 475 (0.21%)	0 / 476 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic cerebral infarction			
subjects affected / exposed	1 / 475 (0.21%)	0 / 476 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	6 / 475 (1.26%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	7 / 12	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow failure			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Anaemia vitamin B12 deficiency			
subjects affected / exposed	1 / 475 (0.21%)	0 / 476 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	2 / 475 (0.42%)	0 / 476 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Hypoacusis			
subjects affected / exposed	1 / 475 (0.21%)	0 / 476 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			
subjects affected / exposed	1 / 475 (0.21%)	0 / 476 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 475 (0.21%)	0 / 476 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders			
Ascites			
subjects affected / exposed	12 / 475 (2.53%)	12 / 476 (2.52%)	
occurrences causally related to treatment / all	5 / 15	8 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 475 (0.42%)	8 / 476 (1.68%)	
occurrences causally related to treatment / all	2 / 2	7 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal varices haemorrhage			
subjects affected / exposed	5 / 475 (1.05%)	7 / 476 (1.47%)	
occurrences causally related to treatment / all	0 / 7	3 / 8	
deaths causally related to treatment / all	0 / 1	0 / 0	
Abdominal pain			
subjects affected / exposed	11 / 475 (2.32%)	6 / 476 (1.26%)	
occurrences causally related to treatment / all	1 / 11	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 475 (0.00%)	6 / 476 (1.26%)	
occurrences causally related to treatment / all	0 / 0	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	2 / 475 (0.42%)	6 / 476 (1.26%)	
occurrences causally related to treatment / all	2 / 5	4 / 7	
deaths causally related to treatment / all	0 / 2	1 / 2	
Duodenal ulcer haemorrhage			
subjects affected / exposed	1 / 475 (0.21%)	3 / 476 (0.63%)	
occurrences causally related to treatment / all	1 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 475 (0.00%)	3 / 476 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			

subjects affected / exposed	0 / 475 (0.00%)	2 / 476 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	0 / 475 (0.00%)	2 / 476 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	1 / 475 (0.21%)	2 / 476 (0.42%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	0 / 475 (0.00%)	2 / 476 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal distension			
subjects affected / exposed	2 / 475 (0.42%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	3 / 475 (0.63%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	3 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal haemorrhage			

subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pancreatitis acute			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Varices oesophageal			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 475 (0.21%)	0 / 476 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	1 / 475 (0.21%)	0 / 476 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food poisoning			
subjects affected / exposed	1 / 475 (0.21%)	0 / 476 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric perforation			
subjects affected / exposed	1 / 475 (0.21%)	0 / 476 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			
subjects affected / exposed	1 / 475 (0.21%)	0 / 476 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			

subjects affected / exposed	2 / 475 (0.42%)	0 / 476 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	2 / 475 (0.42%)	0 / 476 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	1 / 475 (0.21%)	0 / 476 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	2 / 475 (0.42%)	0 / 476 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal haemorrhage			
subjects affected / exposed	1 / 475 (0.21%)	0 / 476 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	8 / 475 (1.68%)	14 / 476 (2.94%)	
occurrences causally related to treatment / all	3 / 11	8 / 22	
deaths causally related to treatment / all	0 / 2	3 / 10	
Jaundice cholestatic			
subjects affected / exposed	4 / 475 (0.84%)	7 / 476 (1.47%)	
occurrences causally related to treatment / all	0 / 4	2 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portal vein thrombosis			
subjects affected / exposed	0 / 475 (0.00%)	4 / 476 (0.84%)	
occurrences causally related to treatment / all	0 / 0	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 2	
Cholangitis			

subjects affected / exposed	2 / 475 (0.42%)	3 / 476 (0.63%)	
occurrences causally related to treatment / all	0 / 2	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatic cirrhosis			
subjects affected / exposed	0 / 475 (0.00%)	3 / 476 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bile duct obstruction			
subjects affected / exposed	0 / 475 (0.00%)	2 / 476 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bile duct stone			
subjects affected / exposed	0 / 475 (0.00%)	2 / 476 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 475 (0.00%)	2 / 476 (0.42%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute hepatic failure			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Biliary dilatation			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	2 / 475 (0.42%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic hepatic failure			

subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haemobilia			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	5 / 475 (1.05%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	5 / 6	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatorenal syndrome			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
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 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocholecystis			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver injury			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			

subjects affected / exposed	4 / 475 (0.84%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Intertrigo			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug eruption			
subjects affected / exposed	2 / 475 (0.42%)	0 / 476 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seborrhoeic dermatitis			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema multiforme			
subjects affected / exposed	1 / 475 (0.21%)	0 / 476 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psoriasis			
subjects affected / exposed	1 / 475 (0.21%)	0 / 476 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	3 / 475 (0.63%)	0 / 476 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Proteinuria			
subjects affected / exposed	0 / 475 (0.00%)	4 / 476 (0.84%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	2 / 475 (0.42%)	3 / 476 (0.63%)	
occurrences causally related to treatment / all	0 / 2	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 475 (0.00%)	2 / 476 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	2 / 475 (0.42%)	2 / 476 (0.42%)	
occurrences causally related to treatment / all	0 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
IgA nephropathy			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal tubular necrosis			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
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	5 / 475 (1.05%)	2 / 476 (0.42%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Muscular weakness			
subjects affected / exposed	1 / 475 (0.21%)	2 / 476 (0.42%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	5 / 475 (1.05%)	2 / 476 (0.42%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	1 / 475 (0.21%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			

subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column stenosis			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
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 / 475 (0.21%)	0 / 476 (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			
Pneumonia			
subjects affected / exposed	5 / 475 (1.05%)	5 / 476 (1.05%)	
occurrences causally related to treatment / all	1 / 7	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	3 / 475 (0.63%)	7 / 476 (1.47%)	
occurrences causally related to treatment / all	0 / 4	2 / 11	
deaths causally related to treatment / all	0 / 1	1 / 5	
Cellulitis			
subjects affected / exposed	0 / 475 (0.00%)	2 / 476 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 475 (0.21%)	2 / 476 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			

subjects affected / exposed	1 / 475 (0.21%)	2 / 476 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 475 (0.21%)	2 / 476 (0.42%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis bacterial			
subjects affected / exposed	0 / 475 (0.00%)	2 / 476 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urinary tract infection			
subjects affected / exposed	0 / 475 (0.00%)	2 / 476 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendiceal abscess			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary tract infection			
subjects affected / exposed	1 / 475 (0.21%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue fever			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			

subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrointestinal viral infection			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin abscess			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 475 (0.21%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious pleural effusion			
subjects affected / exposed	1 / 475 (0.21%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung abscess			
subjects affected / exposed	1 / 475 (0.21%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perihepatic abscess			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periodontitis			

subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural infection			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative abscess			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonellosis			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scrotal infection			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 475 (0.21%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Tuberculosis			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection enterococcal			

subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute sinusitis			
subjects affected / exposed	1 / 475 (0.21%)	0 / 476 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspergillus infection			
subjects affected / exposed	1 / 475 (0.21%)	0 / 476 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 475 (0.21%)	0 / 476 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 475 (0.21%)	0 / 476 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot infection			
subjects affected / exposed	1 / 475 (0.21%)	0 / 476 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 475 (0.21%)	0 / 476 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ophthalmic herpes simplex			

subjects affected / exposed	1 / 475 (0.21%)	0 / 476 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perineal abscess			
subjects affected / exposed	1 / 475 (0.21%)	0 / 476 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia escherichia			
subjects affected / exposed	1 / 475 (0.21%)	0 / 476 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 475 (0.21%)	0 / 476 (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			
Decreased appetite			
subjects affected / exposed	2 / 475 (0.42%)	11 / 476 (2.31%)	
occurrences causally related to treatment / all	1 / 2	8 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	2 / 475 (0.42%)	3 / 476 (0.63%)	
occurrences causally related to treatment / all	0 / 4	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 475 (0.00%)	2 / 476 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 475 (0.00%)	2 / 476 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cachexia			

subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Diabetes mellitus			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoalbuminaemia			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 475 (0.21%)	1 / 476 (0.21%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoproteinaemia			
subjects affected / exposed	1 / 475 (0.21%)	0 / 476 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	0 / 475 (0.00%)	1 / 476 (0.21%)	
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	Sorafenib	Lenvatinib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	469 / 475 (98.74%)	469 / 476 (98.53%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	147 / 475 (30.95%)	200 / 476 (42.02%)	
occurrences (all)	269	419	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	48 / 475 (10.11%)	53 / 476 (11.13%)	
occurrences (all)	84	122	
Fatigue			
subjects affected / exposed	120 / 475 (25.26%)	141 / 476 (29.62%)	
occurrences (all)	170	226	
Oedema peripheral			
subjects affected / exposed	33 / 475 (6.95%)	67 / 476 (14.08%)	
occurrences (all)	45	107	
Pyrexia			
subjects affected / exposed	61 / 475 (12.84%)	63 / 476 (13.24%)	
occurrences (all)	74	79	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	37 / 475 (7.79%)	45 / 476 (9.45%)	
occurrences (all)	46	54	
Dysphonia			
subjects affected / exposed	57 / 475 (12.00%)	113 / 476 (23.74%)	
occurrences (all)	69	134	
Epistaxis			
subjects affected / exposed	15 / 475 (3.16%)	35 / 476 (7.35%)	
occurrences (all)	17	35	
Dyspnoea			
subjects affected / exposed	17 / 475 (3.58%)	31 / 476 (6.51%)	
occurrences (all)	19	39	
Psychiatric disorders			

Insomnia			
subjects affected / exposed	28 / 475 (5.89%)	33 / 476 (6.93%)	
occurrences (all)	34	38	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	51 / 475 (10.74%)	53 / 476 (11.13%)	
occurrences (all)	108	86	
Aspartate aminotransferase increased			
subjects affected / exposed	80 / 475 (16.84%)	64 / 476 (13.45%)	
occurrences (all)	173	128	
Blood alkaline phosphatase increased			
subjects affected / exposed	29 / 475 (6.11%)	32 / 476 (6.72%)	
occurrences (all)	40	59	
Blood bilirubin increased			
subjects affected / exposed	63 / 475 (13.26%)	67 / 476 (14.08%)	
occurrences (all)	128	141	
Electrocardiogram QT prolonged			
subjects affected / exposed	24 / 475 (5.05%)	33 / 476 (6.93%)	
occurrences (all)	62	59	
Gamma-glutamyltransferase increased			
subjects affected / exposed	27 / 475 (5.68%)	37 / 476 (7.77%)	
occurrences (all)	41	60	
Neutrophil count decreased			
subjects affected / exposed	13 / 475 (2.74%)	41 / 476 (8.61%)	
occurrences (all)	21	101	
Platelet count decreased			
subjects affected / exposed	59 / 475 (12.42%)	87 / 476 (18.28%)	
occurrences (all)	127	260	
Weight decreased			
subjects affected / exposed	108 / 475 (22.74%)	149 / 476 (31.30%)	
occurrences (all)	182	290	
White blood cell count decreased			
subjects affected / exposed	25 / 475 (5.26%)	47 / 476 (9.87%)	
occurrences (all)	55	115	
Nervous system disorders			

Headache			
subjects affected / exposed	39 / 475 (8.21%)	45 / 476 (9.45%)	
occurrences (all)	48	57	
Dizziness			
subjects affected / exposed	16 / 475 (3.37%)	29 / 476 (6.09%)	
occurrences (all)	22	33	
Hepatic encephalopathy			
subjects affected / exposed	6 / 475 (1.26%)	24 / 476 (5.04%)	
occurrences (all)	6	37	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	43 / 475 (9.05%)	35 / 476 (7.35%)	
occurrences (all)	104	55	
Thrombocytopenia			
subjects affected / exposed	28 / 475 (5.89%)	33 / 476 (6.93%)	
occurrences (all)	90	81	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	24 / 475 (5.05%)	39 / 476 (8.19%)	
occurrences (all)	27	57	
Abdominal pain			
subjects affected / exposed	83 / 475 (17.47%)	82 / 476 (17.23%)	
occurrences (all)	111	136	
Abdominal pain upper			
subjects affected / exposed	41 / 475 (8.63%)	58 / 476 (12.18%)	
occurrences (all)	59	82	
Ascites			
subjects affected / exposed	39 / 475 (8.21%)	63 / 476 (13.24%)	
occurrences (all)	54	82	
Constipation			
subjects affected / exposed	52 / 475 (10.95%)	76 / 476 (15.97%)	
occurrences (all)	62	95	
Diarrhoea			
subjects affected / exposed	223 / 475 (46.95%)	186 / 476 (39.08%)	
occurrences (all)	448	406	
Dyspepsia			

subjects affected / exposed	18 / 475 (3.79%)	31 / 476 (6.51%)	
occurrences (all)	20	40	
Nausea			
subjects affected / exposed	71 / 475 (14.95%)	90 / 476 (18.91%)	
occurrences (all)	94	131	
Stomatitis			
subjects affected / exposed	56 / 475 (11.79%)	45 / 476 (9.45%)	
occurrences (all)	76	67	
Vomiting			
subjects affected / exposed	37 / 475 (7.79%)	75 / 476 (15.76%)	
occurrences (all)	65	110	
Dry mouth			
subjects affected / exposed	8 / 475 (1.68%)	32 / 476 (6.72%)	
occurrences (all)	8	38	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	120 / 475 (25.26%)	15 / 476 (3.15%)	
occurrences (all)	140	16	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	246 / 475 (51.79%)	128 / 476 (26.89%)	
occurrences (all)	614	236	
Pruritus			
subjects affected / exposed	35 / 475 (7.37%)	34 / 476 (7.14%)	
occurrences (all)	46	41	
Rash			
subjects affected / exposed	77 / 475 (16.21%)	46 / 476 (9.66%)	
occurrences (all)	105	59	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	55 / 475 (11.58%)	117 / 476 (24.58%)	
occurrences (all)	125	363	
Haematuria			
subjects affected / exposed	9 / 475 (1.89%)	25 / 476 (5.25%)	
occurrences (all)	11	34	
Endocrine disorders			

Hypothyroidism			
subjects affected / exposed	8 / 475 (1.68%)	81 / 476 (17.02%)	
occurrences (all)	9	104	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	20 / 475 (4.21%)	42 / 476 (8.82%)	
occurrences (all)	31	52	
Back pain			
subjects affected / exposed	28 / 475 (5.89%)	48 / 476 (10.08%)	
occurrences (all)	30	55	
Musculoskeletal pain			
subjects affected / exposed	25 / 475 (5.26%)	47 / 476 (9.87%)	
occurrences (all)	30	56	
Pain in extremity			
subjects affected / exposed	18 / 475 (3.79%)	38 / 476 (7.98%)	
occurrences (all)	32	59	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	25 / 475 (5.26%)	23 / 476 (4.83%)	
occurrences (all)	33	26	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	126 / 475 (26.53%)	162 / 476 (34.03%)	
occurrences (all)	165	269	
Hypoalbuminaemia			
subjects affected / exposed	38 / 475 (8.00%)	43 / 476 (9.03%)	
occurrences (all)	56	88	
Hypokalaemia			
subjects affected / exposed	26 / 475 (5.47%)	9 / 476 (1.89%)	
occurrences (all)	52	14	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 January 2014	Protocol Amendment 1: Revisions included changes to the inclusion/exclusion criteria and clarification of study conduct/procedures based on feedback from the investigators, addition of safety monitoring procedures as a result of the EU Voluntary Harmonisation Procedure (VHP) for protocol review, and updating of the instruments used to collect HRQoL.
09 April 2014	Protocol Amendment 2: As required by the Japanese regulatory authority (Pharmaceuticals and Medical Devices Agency), clarified that although progression of HCC was not to be reported as a TEAE, if the progression led to an untoward medical occurrence, this untoward medical occurrence was to be reported as a TEAE. Revision of Exclusion Criteria #10 to clarify that subjects who required active interventional treatment of gastric or esophageal varices within 28 days prior to randomization were to be excluded. As required by the French Health authority, clarified toxicity management for sorafenib-treated subjects with QTc prolongation (>=501 msec) and advised caution when using medicines that are known to prolong the QTc interval when used concomitantly with sorafenib.
16 January 2015	Protocol Amendment 3: As requested during the EU VHP review, information on the occurrence, diagnosis, and management of PRES in lenvatinib-treated subjects was added. As requested by the French Health Authority, since the occurrence of PRES was added to the lenvatinib Investigator's Brochure as an "expected" adverse event, any further reports of PRES were no longer subject to expedited reporting to regulatory authorities.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported