Clinical trial results:
A Phase III randomized, double-blind, placebo-controlled study of sorafenib as adjuvant treatment for hepatocellular carcinoma after surgical resection or local ablation

Summary

EudraCT number	2008-001087-36
Trial protocol	SE GB ES AT BE FR IT PT DE GR BG
Global end of trial date	28 November 2014

Results information

Result version number	v3
This version publication date	27 July 2018
First version publication date	24 May 2015
Version creation reason	• New data added to full data set New data added to full data set

Trial information

Trial identification

Sponsor protocol code	BAY43-9006/12414

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00692770
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, Leverkusen, Germany, D-51368
Public contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.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	27 February 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 November 2013
Global end of trial reached?	Yes
Global end of trial date	28 November 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy and safety of sorafenib versus placebo in the adjuvant treatment of hepatocellular carcinoma (HCC) after potentially curative treatment with surgical resection or local ablation.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. A core information and informed consent form was provided. Prior to the beginning of the study, the investigator was required to have the Ethics committee's written approval / favorable opinion of the written informed consent form and any other written information to be provided to subjects. Before entering the study, the informed consent form was read by and explained to all subjects or their legally authorized representative. Each subject had ample opportunity to ask questions and was assured of the right to withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision.
For the collection of images in post-study follow up, the investigator was required to obtain written informed consent from the subject prior to performing any computed tomography / magnetic resonance imaging scan or chest X-ray imaging procedures according to the protocol image acquisition guidelines.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 August 2008
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Portugal: 1
Country: Number of subjects enrolled	Romania: 14
Country: Number of subjects enrolled	Spain: 25
Country: Number of subjects enrolled	Sweden: 7
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	Austria: 17
Country: Number of subjects enrolled	Belgium: 13
Country: Number of subjects enrolled	Bulgaria: 1
Country: Number of subjects enrolled	France: 59
Country: Number of subjects enrolled	Germany: 25

Country: Number of subjects enrolled	Greece: 1
Country: Number of subjects enrolled	Italy: 146
Country: Number of subjects enrolled	Argentina: 3
Country: Number of subjects enrolled	Brazil: 7
Country: Number of subjects enrolled	Canada: 13
Country: Number of subjects enrolled	Chile: 1
Country: Number of subjects enrolled	Mexico: 5
Country: Number of subjects enrolled	United States: 91
Country: Number of subjects enrolled	Australia: 8
Country: Number of subjects enrolled	China: 256
Country: Number of subjects enrolled	Hong Kong: 31
Country: Number of subjects enrolled	Japan: 149
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 126
Country: Number of subjects enrolled	New Zealand: 9
Country: Number of subjects enrolled	Singapore: 13
Country: Number of subjects enrolled	Taiwan: 68
Country: Number of subjects enrolled	Switzerland: 5
Country: Number of subjects enrolled	Russian Federation: 11
Worldwide total number of subjects	1114
EEA total number of subjects	318

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)	744
From 65 to 84 years	369
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Subject recruitment period was between 15 August 2008 to 12 November 2010.

Pre-assignment

Screening details:

Of 1602 participants who were screened for inclusion in the study, 1114 were enrolled, and 1107 received treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Sorafenib (Nexavar, BAY43-9006)

Arm description:

Subjects received 2 tablets of Sorafenib [2*200 milligram (mg)] orally twice daily.

Arm type	Experimental
Investigational medicinal product name	Sorafenib
Investigational medicinal product code	BAY43-9006
Other name	Nexavar
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received an oral dose of sorafenib 400 mg tablets (each containing 200 mg) twice daily, on a continuous basis until a criterion for withdrawal was reached. Doses could be interrupted or reduced due to clinically significant toxicities that were considered related to protocol therapy.

Arm title	Placebo

Arm description:

Subjects received 2 tablets of placebo orally twice daily.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received an oral dose of placebo matching to sorafenib 400 mg tablets (each containing 200 mg) twice daily, on a continuous basis until a criterion for withdrawal was reached. Doses could be interrupted or reduced due to clinically significant toxicities that were considered related to protocol therapy.

Number of subjects in period 1	Sorafenib (Nexavar, BAY43-9006)	Placebo
Started	556	558
Study drug administered	553	554
Completed	82	107
Not completed	474	451
Disease progression, recurrence or relapse	165	274
Protocol driven decision point	3	-
Non-compliant with study medication	11	5
Adverse event	133	41
Radiological and clinical progression	8	8
Consent withdrawn by subject	93	35
Protocol violation	2	7
Randomized but not treated	3	4
Death	10	5
Completed all planned assessments	35	65
Investigator decision not protocol driven	2	1
Lost to follow-up	7	3
Progression by clinical judgment	2	3

Baseline characteristics

Reporting groups	
Reporting group title	Sorafenib (Nexavar, BAY43-9006)
Reporting group description:	
Subjects received 2 tablets of Sorafenib [2*200 milligram (mg)] orally twice daily.	
Reporting group title	Placebo
Reporting group description:	
Subjects received 2 tablets of placebo orally twice daily.	

Reporting group values	Sorafenib (Nexavar, BAY43-9006)	Placebo	Total
Number of subjects	556	558	1114
Age categorical Units: Subjects			
Adults (18-64 years)	383	361	744
From 65-84 years	173	197	370
Age continuous Units: years			
arithmetic mean	58.1	58.7	
standard deviation	± 11.7	± 12.2	-
Gender categorical Units: Subjects			
Female	105	97	202
Male	451	461	912

End points

End points reporting groups

Reporting group title	Sorafenib (Nexavar, BAY43-9006)
Reporting group description:	
Subjects received 2 tablets of Sorafenib [2*200 milligram (mg)] orally twice daily.	
Reporting group title	Placebo
Reporting group description:	
Subjects received 2 tablets of placebo orally twice daily.	

Primary: Recurrence Free Survival (RFS) by Independent Assessment

End point title	Recurrence Free Survival (RFS) by Independent Assessment

End point description:

Disease recurrence of HCC (intra or extra hepatic) was defined as the appearance of a new intrahepatic lesions fulfilling the American Association for the Study of Liver Diseases (AASLD) criteria of diagnosis of HCC or a new extra-hepatic lesions according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria version 1.0. In addition to investigator assessment, all images were reviewed by an independent panel of radiologists. The calculation of the RFS was based on the independent evaluation of the scans.
RFS was defined as the time from randomization to the first documented disease recurrence by independent radiological assessment or death due to any cause whichever occurred first. For subjects who had not recurred or died at the time of analysis, RFS was censored at their last date of evaluable scan before drop-out for any other reason than recurrence or death.

End point type	Primary

End point timeframe:

From randomization up to 4 years or until disease recurrence whichever came first

End point values	Sorafenib (Nexavar, BAY43-9006)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	556	558		
Units: days				
median (confidence interval 95%)	1014 (839 to 1339)	1026 (841 to 1185)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Sorafenib (Nexavar, BAY43-9006) v Placebo

Number of subjects included in analysis	1114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.258329 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	1.134

Notes:

[1] - One sided P-value was stratified by region, risk of recurrence and previous curative treatment.

Secondary: Time to Recurrence (TTR) by Independent Assessment

End point title	Time to Recurrence (TTR) by Independent Assessment

End point description:

TTR was defined as the time from randomization to the first documented disease recurrence by independent radiological assessment. For subjects who had not recurred at the time of analysis, TTR was censored at their last date of evaluable scan before withdrawal for any other reason than recurrence. '99999' in the reported data indicates value could not be estimated due to censored data.

End point type	Secondary

End point timeframe:

From randomization up to 4 years or until disease recurrence whichever came first

End point values	Sorafenib (Nexavar, BAY43-9006)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	556	558		
Units: days				
median (confidence interval 95%)	1172 (924 to 99999)	1089 (923 to 1260)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Sorafenib (Nexavar, BAY43-9006) v Placebo
Number of subjects included in analysis	1114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.121383 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.891

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.735
upper limit	1.081

Notes:

[2] - One-sided P-value was stratified by region, risk of recurrence and previous curative treatment

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time from randomization to date of death due to any cause. OS for subjects alive at the time of analysis was censored at their last date of contact. '99999' in the reported data indicates value could not be estimated due to censored data.

End point type	Secondary

End point timeframe:

From randomization of the first subject until 4 years later.

End point values	Sorafenib (Nexavar, BAY43-9006)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	556	558		
Units: days				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Sorafenib (Nexavar, BAY43-9006) v Placebo
Number of subjects included in analysis	1114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.484742 [3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.995
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.761
upper limit	1.3

Notes:

[3] - One-sided P-value was stratified by region, risk of recurrence and previous curative treatment

Other pre-specified: Patient Reported Outcomes: Euroqol-5 Dimensions (EQ-5D) -

Index Score

End point title	Patient Reported Outcomes: Euroqol-5 Dimensions (EQ-5D) - Index Score

End point description:

The EQ-5D is a generic quality of life preference based on a validated instrument used in cancer and in general population, with 2 parts: Index and Visual Analogue Scale. The EQ-5D Index is a descriptive system of the following health dimensions: mobility, selfcare, usual activities, pain/discomfort, and anxiety/depression. Subjects were asked to choose any one of the 3 response levels for each dimension: no problems, some problems, and severe problems. The 5 health dimensions were summarized into a single score, the EQ-5D Index score which ranged from -0.59 to 1 with higher scores representing better health states (0=death, 1= perfect health, and -0.59=a health state worse than death). A change of at least 0.10 to 0.12 points was considered a minimally important difference using Eastern Cooperative Oncology Group Performance Status as the anchor. The results on the Analysis of covariance of time-adjusted Area under curve for the EQ-5D index score were reported.

End point type	Other pre-specified

End point timeframe:

Cycle (C) Day (D)1, C2D1, C3D1 and subsequent cycles up to C18, end of intervention visit (1 to 2 weeks after last dose)

End point values	Sorafenib (Nexavar, BAY43-9006)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	556	558		
Units: unit on a scale				
least squares mean (confidence interval 95%)	0.827 (0.804 to 0.85)	0.866 (0.843 to 0.888)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

An analysis of covariance (ANCOVA) model was used to estimate the mean difference in the time-adjusted Area Under Curve (AUC) between the two treatment groups, with covariates for baseline scores and stratification factors. To test the treatment effect, a mixed linear model (random coefficient model) was used for the EQ-5D index score. Statistical tests were performed with a 2 sided type I error of 5%.

Comparison groups	Sorafenib (Nexavar, BAY43-9006) v Placebo
Number of subjects included in analysis	1114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference
Point estimate	0.039
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.025
upper limit	0.052

Other pre-specified: Patient Reported Outcomes: Euroqol-5 Dimensions (EQ-5D) - Visual Analogue Scale (VAS) Score

End point title	Patient Reported Outcomes: Euroqol-5 Dimensions (EQ-5D) - Visual Analogue Scale (VAS) Score

End point description:

The EQ-5D is a generic quality of life preference based on a validated instrument used in cancer and in general population, with 2 parts: Index and Visual Analogue Scale. The EQ-5D VAS is a measure that represents health status as a single value. It is a 20-centimetre vertical graduated visual analogue scale with scores that ranged from 0 (worst imaginable health state) to 100 (best imaginable health state). The respondent rated his/her current health state by drawing a line from the box marked 'your own health state today' to the appropriate point on the EQ-5D VAS. A 3-digit number (including leading zeros) was read off the scale from the point where the respondent's line crossed the scale, which was the EQ-5D VAS score. A change of at least 7 points on the VAS was considered as minimally important. The results on the ANCOVA analysis of time-adjusted AUC for the EQ-5D VAS score were reported.

End point type	Other pre-specified

End point timeframe:

Cycle (C) Day (D)1, C2D1, C3D1 and subsequent cycles up to C18, end of intervention visit (1 to 2 weeks after last dose)

End point values	Sorafenib (Nexavar, BAY43-9006)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	556	558		
Units: unit on a scale				
least squares mean (confidence interval 95%)	77.203 (75.184 to 79.223)	80.181 (78.212 to 82.151)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

An analysis of covariance (ANCOVA) model was used to estimate the mean difference in the time-adjusted Area Under Curve (AUC) between the two treatment groups, with covariates for baseline scores and stratification factors. To test the treatment effect, a mixed linear model (random coefficient model) was used for the EQ-5D VAS score. Statistical tests were performed with a 2 sided type I error of 5%.

Comparison groups	Sorafenib (Nexavar, BAY43-9006) v Placebo
Number of subjects included in analysis	1114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference
Point estimate	2.978

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.797
upper limit	4.159

Other pre-specified: Patient Reported Outcomes: Functional Assessment of Cancer Therapy (FACT)-Hepatobiliary Subscale (HEP) Score

End point title	Patient Reported Outcomes: Functional Assessment of Cancer Therapy (FACT)-Hepatobiliary Subscale (HEP) Score

End point description:

The FACT-HEP is a 45 item, self-administered, multi-dimensional, psychometrically sound questionnaire used extensively in oncology clinical trials. FACT-HEP consisted of five subscales: Physical Well-Being (PWB), Social Well-Being (SWB), Emotional Well-Being (EWB), Functional Well-Being (FWB), and Hepatobiliary Cancer Subscale (HCS). The PWB, FWB, SWB and EWB were summed to form the FACT-General (FACT-G) total score. The FACT-G and HCS scores were summed to form the FACT-HEP total score. FACT-HEP scores ranged from 0 to 180 and the higher scores represented a better quality of life. Subjects responded to each item on a 5-point Likert-type scale ranging from 0 (not at all) to 4 (very much). The minimally important difference (MID) for the FACT-Hep total score was in the range of 8 to 9. The results on the ANCOVA analysis of time-adjusted AUC for the FACT-HEP score were reported.

End point type	Other pre-specified

End point timeframe:

Cycle (C) Day (D)1, C2D1, C3D1 and subsequent cycles up to C18, end of intervention visit (1 to 2 weeks after last dose)

End point values	Sorafenib (Nexavar, BAY43-9006)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	556	558		
Units: unit on a scale`				
least squares mean (confidence interval 95%)	138.7 (135.9 to 141.5)	143.79 (141.1 to 146.5)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

An ANCOVA model was used to estimate the mean difference in the time-adjusted AUC between the two treatment groups, with covariates for baseline scores and stratification factors. To test the treatment effect, a mixed linear model (random coefficient model) was used for the FACT-HEP score. Statistical tests were performed with a 2 sided type I error of 5%.

Comparison groups	Sorafenib (Nexavar, BAY43-9006) v Placebo

Number of subjects included in analysis	1114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference
Point estimate	5.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.5
upper limit	6.7

Other pre-specified: Patient Reported Outcomes: Functional Assessment of Cancer Therapy (FACT)-General (G) Total Score

End point title	Patient Reported Outcomes: Functional Assessment of Cancer Therapy (FACT)-General (G) Total Score

End point description:

The PWB, FWB, SWB and EWB were summed to form the FACT-G total score. Subjects responded to each item on a 5-point Likert-type scale ranging from 0 (not at all) to 4 (very much). FACT-G scores ranged from 0 to 108 and the higher scores represented a better quality of life. The MID for the FACT-G total score was in the range of 6 to 7. The results on the ANCOVA analysis of time-adjusted AUC for the FACT-G score were reported.

End point type	Other pre-specified

End point timeframe:

Cycle (C) Day (D)1, C2D1, C3D1 and subsequent cycles up to C18, end of intervention visit (1 to 2 weeks after last dose)

End point values	Sorafenib (Nexavar, BAY43-9006)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	556	558		
Units: unit on a scale				
least squares mean (confidence interval 95%)	80.46 (78.6 to 82.3)	82.95 (81.1 to 84.8)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

An ANCOVA model was used to estimate the mean difference in the time-adjusted AUC between the two treatment groups, with covariates for baseline scores and stratification factors. To test the treatment effect, a mixed linear model (random coefficient model) was used for the FACT-G score. Statistical tests were performed with a 2 sided type I error of 5%.

Comparison groups	Sorafenib (Nexavar, BAY43-9006) v Placebo

Number of subjects included in analysis	1114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference
Point estimate	2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.4
upper limit	3.6

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
After the subject has signed the informed consent, up to 30 days post treatment discontinuation	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups	
Reporting group title	Sorafenib (Nexavar, BAY43-9006)
Reporting group description:	
Subjects received 2 tablets of Sorafenib [2*200 milligram (mg)] orally twice daily.	
Reporting group title	Placebo
Reporting group description:	
Subjects received 2 tablets of placebo orally twice daily.	

Serious adverse events	Sorafenib (Nexavar, BAY43-9006)	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	228 / 559 (40.79%)	230 / 548 (41.97%)	
number of deaths (all causes)	114	131	
number of deaths resulting from adverse events	15	9	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign hepatic neoplasm			
subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			
subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			

subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic myeloid leukaemia			
subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	1 / 559 (0.18%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric cancer			
subjects affected / exposed	1 / 559 (0.18%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemangioma of liver			
subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic neoplasm			
subjects affected / exposed	1 / 559 (0.18%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal squamous cell carcinoma			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to lung			
subjects affected / exposed	1 / 559 (0.18%)	2 / 548 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic pain			

subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-Hodgkin's lymphoma			
subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Oesophageal adenocarcinoma			
subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pancreatic carcinoma			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal adenocarcinoma			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Schwannoma			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin papilloma			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of the hypopharynx			
subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma pancreas			

subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
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	4 / 559 (0.72%)	2 / 548 (0.36%)	
occurrences causally related to treatment / all	1 / 8	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Desmoid tumour			
subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary neoplasm			
subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngeal cancer			
subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lip and/or oral cavity cancer			
subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm recurrence			
subjects affected / exposed	0 / 559 (0.00%)	2 / 548 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm			

subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Huerthle cell carcinoma			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral papilloma			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular carcinoma			
subjects affected / exposed	82 / 559 (14.67%)	130 / 548 (23.72%)	
occurrences causally related to treatment / all	0 / 98	0 / 154	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Arteriovenous fistula			
subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	2 / 559 (0.36%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral vascular disorder			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inferior vena caval occlusion			

subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral embolism			
subjects affected / exposed	1 / 559 (0.18%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Artery dissection			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Incisional hernia repair			
subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm prophylaxis			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Removal of foreign body from gastrointestinal tract			
subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
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	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Chest pain			
subjects affected / exposed	2 / 559 (0.36%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Drowning			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Fatigue			
subjects affected / exposed	3 / 559 (0.54%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	3 / 559 (0.54%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden cardiac death			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coronary artery restenosis			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inflammation			

subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Unevaluable event			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	2 / 559 (0.36%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 559 (0.18%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (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	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			

subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal oedema			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	3 / 559 (0.54%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	0 / 559 (0.00%)	2 / 548 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 559 (0.18%)	4 / 548 (0.73%)	
occurrences causally related to treatment / all	1 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary granuloma			
subjects affected / exposed	2 / 559 (0.36%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			

subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary mass			
subjects affected / exposed	2 / 559 (0.36%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis noninfective			
subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Alcohol abuse			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcoholism			
subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 559 (0.36%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 559 (0.36%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lipase increased			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			
subjects affected / exposed	2 / 559 (0.36%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial injury			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	2 / 559 (0.36%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ligament sprain			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	0 / 559 (0.00%)	3 / 548 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sternal fracture			
subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulna fracture			
subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular injury			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			

subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
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 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Face injury			
subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain contusion			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound evisceration			
subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural bile leak			
subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb crushing injury			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			

subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	2 / 559 (0.36%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 559 (0.18%)	2 / 548 (0.36%)	
occurrences causally related to treatment / all	1 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve stenosis			
subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis coronary artery			
subjects affected / exposed	2 / 559 (0.36%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			

subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	2 / 559 (0.36%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	2 / 559 (0.36%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 559 (0.18%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Left ventricular dysfunction			
subjects affected / exposed	1 / 559 (0.18%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	2 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Carotid artery thrombosis			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebellar haemorrhage			
subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			

subjects affected / exposed	1 / 559 (0.18%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 1	
Cerebral infarction			
subjects affected / exposed	2 / 559 (0.36%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	2 / 559 (0.36%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	3 / 559 (0.54%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Guillain-Barre syndrome			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	2 / 559 (0.36%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			

subjects affected / exposed	3 / 559 (0.54%)	2 / 548 (0.36%)	
occurrences causally related to treatment / all	1 / 7	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive encephalopathy			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord infarction			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 559 (0.18%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			

subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow failure			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tinnitus			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			
subjects affected / exposed	0 / 559 (0.00%)	2 / 548 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	4 / 559 (0.72%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal vein occlusion			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 559 (0.54%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Abdominal pain upper			
subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	3 / 559 (0.54%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crohn's disease			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diaphragmatic hernia, obstructive			
subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 559 (0.36%)	2 / 548 (0.36%)	
occurrences causally related to treatment / all	2 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenitis			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral hernia			

subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			
subjects affected / exposed	1 / 559 (0.18%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	4 / 559 (0.72%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired gastric emptying			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	2 / 559 (0.36%)	3 / 548 (0.55%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal varices haemorrhage			

subjects affected / exposed	4 / 559 (0.72%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	3 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	2 / 559 (0.36%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 559 (0.18%)	2 / 548 (0.36%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 559 (0.00%)	2 / 548 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric volvulus			
subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			

subjects affected / exposed	1 / 559 (0.18%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varices oesophageal			
subjects affected / exposed	2 / 559 (0.36%)	2 / 548 (0.36%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric varices haemorrhage			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal hernia			
subjects affected / exposed	0 / 559 (0.00%)	2 / 548 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised intraabdominal fluid collection			
subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary fistula			
subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	0 / 559 (0.00%)	2 / 548 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis acute			

subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	2 / 559 (0.36%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	4 / 559 (0.72%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	9 / 9	2 / 2	
deaths causally related to treatment / all	3 / 3	0 / 0	
Hepatorenal syndrome			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Jaundice cholestatic			
subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portal vein thrombosis			
subjects affected / exposed	2 / 559 (0.36%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	4 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stenosis			

subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic mass			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biloma			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver injury			
subjects affected / exposed	2 / 559 (0.36%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermal cyst			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis allergic			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (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	10 / 559 (1.79%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	11 / 11	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pruritus			

subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	2 / 559 (0.36%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Telangiectasia			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	2 / 559 (0.36%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 559 (0.00%)	2 / 548 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrotic syndrome			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			

subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
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 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal failure acute			
subjects affected / exposed	2 / 559 (0.36%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric obstruction			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic nephropathy			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (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	1 / 559 (0.18%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone formation increased			
subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Exostosis			

subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gouty arthritis			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 559 (0.18%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 559 (0.00%)	2 / 548 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondylolisthesis			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (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			
Appendicitis			
subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			

subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (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	3 / 559 (0.54%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis B			
subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatitis C			
subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			

subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 559 (0.36%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 559 (0.18%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 559 (0.18%)	2 / 548 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superinfection			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculosis			

subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 559 (0.18%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 559 (0.36%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal abscess			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary sepsis			
subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute hepatitis B			
subjects affected / exposed	0 / 559 (0.00%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Abdominal abscess			

subjects affected / exposed	0 / 559 (0.00%)	3 / 548 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis bacterial			
subjects affected / exposed	1 / 559 (0.18%)	1 / 548 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected dermal cyst			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious pleural effusion			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (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			
Dehydration			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	0 / 559 (0.00%)	2 / 548 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoalbuminaemia			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (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 / 559 (0.00%)	2 / 548 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (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	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 559 (0.18%)	0 / 548 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Sorafenib (Nexavar, BAY43-9006)	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	522 / 559 (93.38%)	360 / 548 (65.69%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	54 / 559 (9.66%)	38 / 548 (6.93%)	
occurrences (all)	251	177	
Aspartate aminotransferase increased			
subjects affected / exposed	51 / 559 (9.12%)	35 / 548 (6.39%)	
occurrences (all)	226	188	
Platelet count decreased			
subjects affected / exposed	48 / 559 (8.59%)	26 / 548 (4.74%)	
occurrences (all)	300	202	
Weight decreased			
subjects affected / exposed	60 / 559 (10.73%)	13 / 548 (2.37%)	
occurrences (all)	254	41	

Weight increased			
subjects affected / exposed	14 / 559 (2.50%)	42 / 548 (7.66%)	
occurrences (all)	68	310	
Vascular disorders			
Hypertension			
subjects affected / exposed	142 / 559 (25.40%)	65 / 548 (11.86%)	
occurrences (all)	869	331	
Nervous system disorders			
Headache			
subjects affected / exposed	40 / 559 (7.16%)	33 / 548 (6.02%)	
occurrences (all)	111	108	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	29 / 559 (5.19%)	14 / 548 (2.55%)	
occurrences (all)	217	97	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	83 / 559 (14.85%)	66 / 548 (12.04%)	
occurrences (all)	315	300	
Pyrexia			
subjects affected / exposed	33 / 559 (5.90%)	24 / 548 (4.38%)	
occurrences (all)	39	32	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	55 / 559 (9.84%)	46 / 548 (8.39%)	
occurrences (all)	156	115	
Abdominal pain upper			
subjects affected / exposed	28 / 559 (5.01%)	14 / 548 (2.55%)	
occurrences (all)	75	36	
Ascites			
subjects affected / exposed	39 / 559 (6.98%)	19 / 548 (3.47%)	
occurrences (all)	145	67	
Constipation			
subjects affected / exposed	41 / 559 (7.33%)	36 / 548 (6.57%)	
occurrences (all)	105	122	
Diarrhoea			

subjects affected / exposed	242 / 559 (43.29%)	64 / 548 (11.68%)	
occurrences (all)	1201	186	
Dyspepsia			
subjects affected / exposed	20 / 559 (3.58%)	30 / 548 (5.47%)	
occurrences (all)	112	125	
Nausea			
subjects affected / exposed	50 / 559 (8.94%)	24 / 548 (4.38%)	
occurrences (all)	119	45	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	30 / 559 (5.37%)	44 / 548 (8.03%)	
occurrences (all)	76	116	
Dysphonia			
subjects affected / exposed	41 / 559 (7.33%)	3 / 548 (0.55%)	
occurrences (all)	133	7	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	187 / 559 (33.45%)	18 / 548 (3.28%)	
occurrences (all)	750	65	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	390 / 559 (69.77%)	27 / 548 (4.93%)	
occurrences (all)	2196	139	
Pruritus			
subjects affected / exposed	47 / 559 (8.41%)	58 / 548 (10.58%)	
occurrences (all)	133	263	
Rash			
subjects affected / exposed	95 / 559 (16.99%)	45 / 548 (8.21%)	
occurrences (all)	296	126	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	24 / 559 (4.29%)	31 / 548 (5.66%)	
occurrences (all)	111	178	
Musculoskeletal and connective tissue disorders			
Arthralgia			

subjects affected / exposed	34 / 559 (6.08%)	30 / 548 (5.47%)	
occurrences (all)	162	139	
Back pain			
subjects affected / exposed	43 / 559 (7.69%)	37 / 548 (6.75%)	
occurrences (all)	152	192	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	30 / 559 (5.37%)	38 / 548 (6.93%)	
occurrences (all)	66	69	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	40 / 559 (7.16%)	18 / 548 (3.28%)	
occurrences (all)	104	52	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 May 2008	Amendment 1 dated 26 MAY 2008 (IND modification serial number 2656) - Removed tumor block sampling - Minor clarifications of inclusion and exclusion criteria - Added PK sampling - Clarified that randomization codes for investigators or pharmacists would be managed by the IVRS system - Clarified end of post study follow-up - Clarified study medication storage conditions
12 June 2008	Amendment 2 (local amendment for Japan), dated 12 JUN 2008 - Japan specific changes with regard to AE monitoring, SAEs, unexpected AEs, ethics committees, identity of investigational products and premature termination of the study/closure of a center.
01 May 2009	Amendment 3 dated 1 MAY 2009 (IND modification serial number 2776) - Increased cap for Asia Pacific patients from 450 to 550 patients allowing a balanced enrollment compared with Western patients while taking into account the higher prevalence of HCC patients in the Asia Pacific region compared with the rest of the world. - Clarified timing definitions for inclusion/exclusion criteria - Clarified exclusion criteria definition regarding potential transplant patients - Clarified study medication storage conditions for blister pack used in the Asia Pacific region - Amended criteria for serious adverse events (SAE) reporting in case of hospitalization in line with updated procedures
02 October 2009	Amendment 4 dated 2 OCT 2009 (IND modification serial number2805) - Expanded time window for time from surgery/ablation to eligibility CT or MRI scan: The additional time beyond the targeted 4 weeks from curative treatment to eligibility scan was expanded to ensure maximum recovery time from curative treatment, while maintaining a short enough timeframe from curative treatment to commencing adjuvant treatment to derive maximum adjuvant treatment benefit. The minimum time of 3 weeks (21 days) was maintained to ensure a valid assessment of the remission status. - Clarified ablation definitions to allow a combination of percutaneous ethanol injection (PEI) and percutaneous or intraoperative radiofrequency ablation (RFA)
11 February 2010	Amendment 5 dated 11 FEB 2010 (IND modification serial number 2870) - Removed Asia Pacific cap: This was done in order to allow completely competitive enrolment across all geographical regions. This was decided based on a blinded inspection of patients' safety profiles, treatment duration, and frequency of discontinuation that did not reveal any unexpected issues or concerns and confirmed that no relevant differences regarding these parameters could be observed across geographical regions. It was therefore considered appropriate to allow complete competitive enrolment into the study and to remove the predefined recruitment cap on the Asia-Pacific region. In addition, it was thought that this would allow a representative ethnical distribution across the regions. It was further considered that despite removing the cap on Asian patients, that the large overall sample size of 1100 subjects would still allow a sufficiently large number of Western patients, which was expected to be greater than 400 subjects.

26 January 2011	Amendment 6 dated 26 JAN 2011 (for all countries other than the USA) (IND modification serial number 2999) - Allowed the continuation of collection of CT/MRI scans beyond premature termination of treatment, into the Post Study Follow Up - Statistical section was modified to state that recurrence events observed from scans collected during post study follow up would be used in the primary analysis. This was done because it was thought that the additional scan evaluations collected post study would reduce the censoring rate and therefore reduce the possibility of biasing the results of the primary endpoint.
31 May 2011	Amendment 8 dated 31 MAY 2011 (for USA only) (IND modification serial number3033) - Following feedback from FDA regarding protocol amendment 6, this amendment stated that recurrence events observed from scans collected during post study follow up would not be used in the primary analysis. This data would be used for supportive sensitivity analyses only.
31 May 2011	Amendment 9 dated 31 MAY 2011 (for all countries other than the USA) - Following feedback from FDA regarding protocol amendment 6, this amendment stated that recurrence events observed from scans collected during post study follow up would not be used in the primary analysis. This data would be used for supportive sensitivity analyses only.
20 June 2012	Amendment 10, dated 20 JUN 2012 (applicable to all countries) (IND modification serial number 3120) - Power of the primary end point reduced from 90% to 80%, thereby reducing the number of centrally confirmed recurrences required from 611 to 457. It was decided that this change would shorten the duration of the study and thereby reduce the amount of missing data due to patient drop-outs. - Clarification was included, stating that 4 years was equal to 204 weeks and that patients who reached 4 years on treatment would continue to be followed for recurrence during follow up. CT/MRI scans were to be performed every 6 months per study image acquisition guidelines. Any recurrences observed in this group of patients could then be included in the primary analysis. - For patients who discontinued treatment prematurely and continued scan collection during follow up (according to amendment 6), the frequency of scan collection was to decrease from 3 monthly to 6 monthly once the patient reached their date of randomization + 204 weeks. Recurrences observed during follow up for patients who withdrew prematurely from treatment (per protocol amendment 6) were still not to be included in the primary analysis (per amendments 8 and 9).
06 August 2012	Amendment 11, dated 6 AUG 2012 (applicable to all countries) (IND modification serial number 3120) - Administrative only - corrects inconsistency within protocol amendment 10

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Decimal places were automatically truncated if last decimal equals zero.

Notes: