Clinical trial results:
A phase III randomized sequential open-label study to evaluate the efficacy and safety of sorafenib followed by sunitinib versus sunitinib followed by sorafenib in the treatment of first-line advanced / metastatic renal cell carcinoma

Summary

EudraCT number	2008-005011-18
Trial protocol	NL DE AT
Global end of trial date	31 October 2013

Results information

Result version number	v1 (current)
This version publication date	13 January 2017
First version publication date	13 January 2017

Trial information

Trial identification

Sponsor protocol code	09072008-13772

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00732914
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Deutsche Krebsgesellschaft Sponsor GmbH
Sponsor organisation address	Staudernheimer Str. 17, Odernheim am Glan, Germany, 55571
Public contact	Projektmanagement, Deutsche Krebsgesellschaft Sponsor GmbH, 49 30 322932935, neugebauer@krebsgesellschaft.de
Scientific contact	Bereich Klinische Studien, Deutsche Krebsgesellschaft e. V., 49 30 322932935, neugebauer@krebsgesellschaft.de

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	03 April 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 October 2013
Global end of trial reached?	Yes
Global end of trial date	31 October 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary:
To evaluate if progression-free survival from randomization to progression or death during second-line therapy (total PFS) of sorafenib followed by sunitinib is at least as effective as sunitinib followed by sorafenib

Protection of trial subjects:

This study was conducted in compliance with local legal and regulatory requirements and in conformance with Good Clinical Practice standards. All subjects were fully informed about nature, scope and possible consequences of the clinical trial in a language appropriate for the subject.

Background therapy: -

Evidence for comparator: -

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

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 48
Country: Number of subjects enrolled	Austria: 29
Country: Number of subjects enrolled	Germany: 288
Worldwide total number of subjects	365
EEA total number of subjects	365

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)	182

From 65 to 84 years	183
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was performed in 96 centers in three countries (Germany, Austria, Netherlands). A total of 365 patients were enrolled between 19 Feb 2009 and 30 Dec 2011.

Pre-assignment

Screening details:

The following steps were performed before randomization: check for inclusion/exclusion criteria, contraindications, medical history of the subjects and signing informed consent forms.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Sorafenib followed by sunitinib

Arm description:

In the experimental group (Group A), patients took per oral 400 mg of sorafenib twice daily (BID) until DP (first-line treatment) followed by 50 mg of sunitinib once daily (QD) in cycles of 6 weeks (4 weeks on and 2 weeks off)

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

Dosage and administration details:

400 mg (2 x 200 mg tablets) taken twice daily

Investigational medicinal product name	Sutent®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Other use

Dosage and administration details:

50 mg per oral taken daily for 4 consecutive weeks, followed by a 2-week rest period (schedule 4/2) to comprise a complete cycle of 6 weeks.

Arm title	Sunitinib followed by sorafenib

Arm description:

In the control group (Group B), patients took per oral 50 mg of sunitinib QD in cycles of 6 weeks (4 weeks on and 2 weeks off) until DP (first-line treatment) followed by 400 mg of sorafenib BID (second-line treatment)

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

Dosage and administration details:

400 mg (2 x 200 mg tablets) taken twice daily

Investigational medicinal product name	Sutent®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Other use

Dosage and administration details:

50 mg per oral taken daily for 4 consecutive weeks, followed by a 2-week rest period (schedule 4/2) to comprise a complete cycle of 6 weeks.

Number of subjects in period 1	Sorafenib followed by sunitinib	Sunitinib followed by sorafenib
Started	182	183
Sorafenib treatment	177	76
Sunitinib treatment	103	176
Completed	0	0
Not completed	182	183
Consent withdrawn by subject	8	7
Physician decision	3	4
Study closed, patient stops study medication	1	-
Other reason	25	31
Patient died	74	69
Lost to follow-up	8	7
Screening failure / no randomization	1	-
Reason missing	62	65

Baseline characteristics

Reporting groups	
Reporting group title	Sorafenib followed by sunitinib
Reporting group description:	
In the experimental group (Group A), patients took per oral 400 mg of sorafenib twice daily (BID) until DP (first-line treatment) followed by 50 mg of sunitinib once daily (QD) in cycles of 6 weeks (4 weeks on and 2 weeks off)	
Reporting group title	Sunitinib followed by sorafenib
Reporting group description:	
In the control group (Group B), patients took per oral 50 mg of sunitinib QD in cycles of 6 weeks (4 weeks on and 2 weeks off) until DP (first-line treatment) followed by 400 mg of sorafenib BID (second-line treatment)	

Reporting group values	Sorafenib followed by sunitinib	Sunitinib followed by sorafenib	Total
Number of subjects	182	183	365
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
median	64	65	
full range (min-max)	39 to 84	40 to 83	-
Gender categorical			
Units: Subjects			
Female	43	48	91
Male	139	135	274
MSKCC risk score			
Memorial Sloan Kettering Cancer Center			
Units: Subjects			
High	1	1	2
Intermediate	108	94	202
Low	71	82	153
Unknown	2	4	6
Missing	0	2	2

End points

End points reporting groups

Reporting group title	Sorafenib followed by sunitinib

Reporting group description:

In the experimental group (Group A), patients took per oral 400 mg of sorafenib twice daily (BID) until DP (first-line treatment) followed by 50 mg of sunitinib once daily (QD) in cycles of 6 weeks (4 weeks on and 2 weeks off)

Reporting group title	Sunitinib followed by sorafenib

Reporting group description:

In the control group (Group B), patients took per oral 50 mg of sunitinib QD in cycles of 6 weeks (4 weeks on and 2 weeks off) until DP (first-line treatment) followed by 400 mg of sorafenib BID (second-line treatment)

Primary: Total Progression-free Survival

End point title	Total Progression-free Survival

End point description:

End point type	Primary

End point timeframe:

Progression-free survival from first treatment to progression or death during second-line therapy (total PFS)

End point values	Sorafenib followed by sunitinib	Sunitinib followed by sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177	176		
Units: days				
median (confidence interval 95%)	379 (298 to 474)	431 (292 to 524)		

Statistical analyses

Statistical analysis title	Analysis of Primary Endpoint

Statistical analysis description:

The primary endpoint is to evaluate if total PFS of sorafenib followed by sunitinib is superior compared to sunitinib followed by sorafenib. A Comparison between the two treatment groups was performed on basis of Kaplan-Meier estimates.

Comparison groups	Sorafenib followed by sunitinib v Sunitinib followed by sorafenib

Number of subjects included in analysis	353
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5398
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.014
Confidence interval	
level	95 %
sides	1-sided
upper limit	1.266

Secondary: Total Time to Progression (TTP)

End point title	Total Time to Progression (TTP)

End point description:

End point type	Secondary

End point timeframe:

Time from first treatment to progression during second-line therapy (total time to progression [TTP])

End point values	Sorafenib followed by sunitinib	Sunitinib followed by sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	182	183		
Units: days	455	521		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First-line Treatment Failure

End point title	Time to First-line Treatment Failure

End point description:

End point type	Secondary

End point timeframe:

Time to first-line treatment failure (progression, death, discontinuation due to toxicity) descriptively in each group

End point values	Sorafenib followed by sunitinib	Sunitinib followed by sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177	176		
Units: days	181	267		

Statistical analyses

No statistical analyses for this end point

Secondary: PFS in First-line Treatment

End point title	PFS in First-line Treatment

End point description:

End point type	Secondary

End point timeframe:

Progression-free survival in first-line treatment

End point values	Sorafenib followed by sunitinib	Sunitinib followed by sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177	176		
Units: days	174	266		

Statistical analyses

No statistical analyses for this end point

Secondary: PFS in Second-line Treatment

End point title	PFS in Second-line Treatment

End point description:

End point type	Secondary

End point timeframe:

Progression-free survival in second-line treatment

End point values	Sorafenib followed by sunitinib	Sunitinib followed by sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177	176		
Units: days	164	85		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

End point type	Secondary

End point timeframe:

Overall survival, descriptively (data cut-off same as for primary endpoint)

End point values	Sorafenib followed by sunitinib	Sunitinib followed by sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177	176		
Units: days	959	907		

Statistical analyses

No statistical analyses for this end point

Secondary: Response Rates and Disease Control Rate - First-line treatment

End point title	Response Rates and Disease Control Rate - First-line treatment

End point description:

End point type	Secondary

End point timeframe:

Disease control rate (DCR); Response rates in first-line treatment (complete response (CR), partial response (PR), stable disease (SD) according to RECIST)

End point values	Sorafenib followed by sunitinib	Sunitinib followed by sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177	176		
Units: percent				
number (not applicable)				
Complete Response (CR)	0.028	0.034		
Partial Response (PR)	0.282	0.256		
Stable Disease (SD)	0.384	0.347		
Disease Control Rate (CDR)	0.695	0.636		

Statistical analyses

No statistical analyses for this end point

Secondary: Response Rates and Disease Control Rate - Second-line treatment

End point title	Response Rates and Disease Control Rate - Second-line treatment

End point description:

End point type	Secondary

End point timeframe:

Disease control rate (DCR); Response rates in second-line treatment (complete response (CR), partial response (PR), stable disease (SD) according to RECIST)

End point values	Sorafenib followed by sunitinib	Sunitinib followed by sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103	76		
Units: percent				
number (not applicable)				
Complete Response (CR)	0.01	0.013		
Partial Response (PR)	0.165	0.053		
Stable Disease (SD)	0.311	0.25		
Disease Control Rate (DCR)	0.485	0.316		

Statistical analyses

No statistical analyses for this end point

Secondary: Response Rates and Disease Control Rate - Overall

End point title	Response Rates and Disease Control Rate - Overall

End point description:

End point type	Secondary

End point timeframe:

Disease control rate (DCR); Response rates overall (complete response (CR), partial response (PR), stable disease (SD) according to RECIST)

End point values	Sorafenib followed by sunitinib	Sunitinib followed by sorafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177	176		
Units: percent				
number (not applicable)				
Complete Response (CR)	0.034	0.04		
Partial Response (PR)	0.328	0.267		
Stable Disease (SD)	0.356	0.364		
Disease Control Rate (DCR)	0.718	0.67		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On treatment and post treatment

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Sorafenib followed by sunitinib

Reporting group description:

In the experimental group (Group A), patients took per oral 400 mg of sorafenib twice daily (BID) until DP (first-line treatment) followed by 50 mg of sunitinib once daily (QD) in cycles of 6 weeks (4 weeks on and 2 weeks off)

Reporting group title	Sunitinib followed by sorafenib

Reporting group description:

In the control group (Group B), patients took per oral 50 mg of sunitinib QD in cycles of 6 weeks (4 weeks on and 2 weeks off) until DP (first-line treatment) followed by 400 mg of sorafenib BID (second-line treatment)

Serious adverse events	Sorafenib followed by sunitinib	Sunitinib followed by sorafenib	
Total subjects affected by serious adverse events			
subjects affected / exposed	111 / 177 (62.71%)	93 / 176 (52.84%)	
number of deaths (all causes)	17	26	
number of deaths resulting from adverse events	2	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	3 / 177 (1.69%)	2 / 176 (1.14%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 1	
Metastases to meninges			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastasis			
subjects affected / exposed	1 / 177 (0.56%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hair follicle tumour benign			

subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	2 / 177 (1.13%)	4 / 176 (2.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 2	
Tumour haemorrhage			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Neoplasm progression			
subjects affected / exposed	0 / 177 (0.00%)	3 / 176 (1.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Basal cell carcinoma			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour necrosis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bone			
subjects affected / exposed	1 / 177 (0.56%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to spine			

subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign pancreatic neoplasm			
subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac myxoma			
subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 177 (2.26%)	6 / 176 (3.41%)	
occurrences causally related to treatment / all	3 / 5	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial occlusive disease			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic venous thrombosis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	2 / 177 (1.13%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			

subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			
subjects affected / exposed	2 / 177 (1.13%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Knee arthroplasty			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery stent insertion			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hysterectomy			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracotomy			
subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoadjuvant therapy			
subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour excision			

subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central venous catheterisation			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenectomy			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (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			
Chest pain			
subjects affected / exposed	2 / 177 (1.13%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Malaise			
subjects affected / exposed	2 / 177 (1.13%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			
subjects affected / exposed	2 / 177 (1.13%)	13 / 176 (7.39%)	
occurrences causally related to treatment / all	0 / 3	0 / 13	
deaths causally related to treatment / all	0 / 1	0 / 11	
Pyrexia			
subjects affected / exposed	3 / 177 (1.69%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	7 / 177 (3.95%)	3 / 176 (1.70%)	
occurrences causally related to treatment / all	2 / 7	2 / 3	
deaths causally related to treatment / all	0 / 2	0 / 0	
Oedema			

subjects affected / exposed	1 / 177 (0.56%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	3 / 177 (1.69%)	4 / 176 (2.27%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	1 / 177 (0.56%)	2 / 176 (1.14%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 177 (0.56%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Death			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Spinal pain			
subjects affected / exposed	2 / 177 (1.13%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 177 (0.56%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernia			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			

subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device dislocation			
subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (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			
Menorrhagia			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	2 / 177 (1.13%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (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	2 / 177 (1.13%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	3 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 177 (0.00%)	3 / 176 (1.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	2 / 177 (1.13%)	2 / 176 (1.14%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 177 (0.00%)	2 / 176 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial obstruction			
subjects affected / exposed	0 / 177 (0.00%)	2 / 176 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Disorientation			
subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
N-terminal prohormone brain natriuretic peptide increased			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood pressure increased			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			
subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriogram coronary			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Imaging procedure			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 177 (0.56%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Femoral neck fracture			
subjects affected / exposed	2 / 177 (1.13%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (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	2 / 177 (1.13%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament sprain			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound			
subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous haematoma			
subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic haematoma			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			

subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 177 (0.56%)	2 / 176 (1.14%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 177 (0.56%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 177 (0.00%)	3 / 176 (1.70%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular extrasystoles			
subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	
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	0 / 177 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 177 (0.56%)	4 / 176 (2.27%)	
occurrences causally related to treatment / all	0 / 1	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrospinal fluid leakage			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	2 / 177 (1.13%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraplegia			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphasia			
subjects affected / exposed	2 / 177 (1.13%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiplegia			

subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (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	2 / 177 (1.13%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	2 / 177 (1.13%)	2 / 176 (1.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial seizures			
subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paresis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	2 / 177 (1.13%)	2 / 176 (1.14%)	
occurrences causally related to treatment / all	2 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Thalamic infarction			

subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Monoparesis			
subjects affected / exposed	1 / 177 (0.56%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebellar haemorrhage			
subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Guillain-Barre syndrome			
subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	1 / 177 (0.56%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	4 / 177 (2.26%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	2 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			

subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic vein thrombosis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 177 (0.56%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual impairment			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyphaema			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal artery occlusion			
subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papilloedema			
subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Melaena			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 177 (0.56%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 177 (1.13%)	3 / 176 (1.70%)	
occurrences causally related to treatment / all	3 / 3	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 177 (0.56%)	3 / 176 (1.70%)	
occurrences causally related to treatment / all	1 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	3 / 177 (1.69%)	4 / 176 (2.27%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 177 (1.13%)	4 / 176 (2.27%)	
occurrences causally related to treatment / all	2 / 2	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 177 (0.56%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			

subjects affected / exposed	2 / 177 (1.13%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 177 (0.56%)	2 / 176 (1.14%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			

subjects affected / exposed	1 / 177 (0.56%)	2 / 176 (1.14%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	2 / 177 (1.13%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis chronic			
subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum intestinal haemorrhagic			
subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticular perforation			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			

subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	2 / 177 (1.13%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	1 / 177 (0.56%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocholecystis			
subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic haemorrhage			
subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	3 / 177 (1.69%)	3 / 176 (1.70%)	
occurrences causally related to treatment / all	3 / 3	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Urticaria			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis allergic			
subjects affected / exposed	1 / 177 (0.56%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug eruption			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash generalised			
subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angioedema			
subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Prerenal failure			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	3 / 177 (1.69%)	3 / 176 (1.70%)	
occurrences causally related to treatment / all	0 / 3	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urinary retention			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proteinuria			

subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Toxic nodular goitre			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroiditis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (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			
Pathological fracture			
subjects affected / exposed	2 / 177 (1.13%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis reactive			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	2 / 177 (1.13%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Neck pain			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column stenosis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteolysis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteitis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pyelonephritis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	9 / 177 (5.08%)	7 / 176 (3.98%)	
occurrences causally related to treatment / all	2 / 9	1 / 7	
deaths causally related to treatment / all	0 / 3	0 / 1	
Anal abscess			
subjects affected / exposed	1 / 177 (0.56%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periumbilical abscess			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intertrigo			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Serratia infection			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 177 (0.56%)	3 / 176 (1.70%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastroenteritis			
subjects affected / exposed	2 / 177 (1.13%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			

subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 177 (0.56%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Diverticulitis			
subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess jaw			
subjects affected / exposed	2 / 177 (1.13%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 177 (0.56%)	4 / 176 (2.27%)	
occurrences causally related to treatment / all	1 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			

subjects affected / exposed	1 / 177 (0.56%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			
subjects affected / exposed	2 / 177 (1.13%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	1 / 177 (0.56%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	3 / 177 (1.69%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	3 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 177 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	0 / 177 (0.00%)	1 / 176 (0.57%)	
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 followed by sunitinib	Sunitinib followed by sorafenib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	172 / 177 (97.18%)	172 / 176 (97.73%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	65 / 177 (36.72%)	64 / 176 (36.36%)	
occurrences (all)	83	73	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	9 / 177 (5.08%)	6 / 176 (3.41%)	
occurrences (all)	9	7	
Asthenia			
subjects affected / exposed	11 / 177 (6.21%)	8 / 176 (4.55%)	
occurrences (all)	12	9	
Disease progression			
subjects affected / exposed	2 / 177 (1.13%)	15 / 176 (8.52%)	
occurrences (all)	3	15	
Fatigue			
subjects affected / exposed	71 / 177 (40.11%)	77 / 176 (43.75%)	
occurrences (all)	110	107	
General physical health deterioration			
subjects affected / exposed	13 / 177 (7.34%)	13 / 176 (7.39%)	
occurrences (all)	21	17	
Mucosal inflammation			
subjects affected / exposed	21 / 177 (11.86%)	34 / 176 (19.32%)	
occurrences (all)	28	48	
Oedema			
subjects affected / exposed	9 / 177 (5.08%)	10 / 176 (5.68%)	
occurrences (all)	11	17	
Oedema peripheral			
subjects affected / exposed	14 / 177 (7.91%)	8 / 176 (4.55%)	
occurrences (all)	20	14	
Pain			
subjects affected / exposed	42 / 177 (23.73%)	27 / 176 (15.34%)	
occurrences (all)	51	38	
Pyrexia			

subjects affected / exposed	24 / 177 (13.56%)	15 / 176 (8.52%)	
occurrences (all)	27	15	
Unevaluable event			
subjects affected / exposed	9 / 177 (5.08%)	11 / 176 (6.25%)	
occurrences (all)	17	17	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	19 / 177 (10.73%)	24 / 176 (13.64%)	
occurrences (all)	21	29	
Dysphonia			
subjects affected / exposed	19 / 177 (10.73%)	10 / 176 (5.68%)	
occurrences (all)	22	12	
Dyspnoea			
subjects affected / exposed	20 / 177 (11.30%)	25 / 176 (14.20%)	
occurrences (all)	23	34	
Epistaxis			
subjects affected / exposed	15 / 177 (8.47%)	20 / 176 (11.36%)	
occurrences (all)	19	24	
Psychiatric disorders			
Depression			
subjects affected / exposed	9 / 177 (5.08%)	9 / 176 (5.11%)	
occurrences (all)	12	9	
Insomnia			
subjects affected / exposed	9 / 177 (5.08%)	14 / 176 (7.95%)	
occurrences (all)	11	14	
Investigations			
Weight decreased			
subjects affected / exposed	28 / 177 (15.82%)	21 / 176 (11.93%)	
occurrences (all)	31	23	
Nervous system disorders			
Dizziness			
subjects affected / exposed	15 / 177 (8.47%)	13 / 176 (7.39%)	
occurrences (all)	18	16	
Dysgeusia			
subjects affected / exposed	24 / 177 (13.56%)	41 / 176 (23.30%)	
occurrences (all)	35	57	

Headache			
subjects affected / exposed	20 / 177 (11.30%)	26 / 176 (14.77%)	
occurrences (all)	33	34	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	17 / 177 (9.60%)	8 / 176 (4.55%)	
occurrences (all)	22	19	
Leukopenia			
subjects affected / exposed	2 / 177 (1.13%)	10 / 176 (5.68%)	
occurrences (all)	27	14	
Thrombocytopenia			
subjects affected / exposed	3 / 177 (1.69%)	11 / 176 (6.25%)	
occurrences (all)	7	23	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	13 / 177 (7.34%)	13 / 176 (7.39%)	
occurrences (all)	19	16	
Abdominal pain upper			
subjects affected / exposed	11 / 177 (6.21%)	11 / 176 (6.25%)	
occurrences (all)	11	15	
Constipation			
subjects affected / exposed	23 / 177 (12.99%)	19 / 176 (10.80%)	
occurrences (all)	31	21	
Diarrhoea			
subjects affected / exposed	101 / 177 (57.06%)	84 / 176 (47.73%)	
occurrences (all)	220	179	
Dry mouth			
subjects affected / exposed	4 / 177 (2.26%)	12 / 176 (6.82%)	
occurrences (all)	4	13	
Dyspepsia			
subjects affected / exposed	21 / 177 (11.86%)	31 / 176 (17.61%)	
occurrences (all)	29	41	
Nausea			
subjects affected / exposed	50 / 177 (28.25%)	57 / 176 (32.39%)	
occurrences (all)	83	76	
Stomatitis			

subjects affected / exposed	23 / 177 (12.99%)	38 / 176 (21.59%)	
occurrences (all)	39	58	
Vomiting			
subjects affected / exposed	26 / 177 (14.69%)	38 / 176 (21.59%)	
occurrences (all)	46	56	
Hepatobiliary disorders			
Jaundice			
subjects affected / exposed	1 / 177 (0.56%)	9 / 176 (5.11%)	
occurrences (all)	1	9	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	57 / 177 (32.20%)	13 / 176 (7.39%)	
occurrences (all)	67	14	
Dry skin			
subjects affected / exposed	21 / 177 (11.86%)	16 / 176 (9.09%)	
occurrences (all)	22	17	
Erythema			
subjects affected / exposed	19 / 177 (10.73%)	10 / 176 (5.68%)	
occurrences (all)	20	11	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	70 / 177 (39.55%)	49 / 176 (27.84%)	
occurrences (all)	124	95	
Pruritus			
subjects affected / exposed	23 / 177 (12.99%)	19 / 176 (10.80%)	
occurrences (all)	45	19	
Rash			
subjects affected / exposed	54 / 177 (30.51%)	22 / 176 (12.50%)	
occurrences (all)	71	30	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	13 / 177 (7.34%)	18 / 176 (10.23%)	
occurrences (all)	13	19	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	21 / 177 (11.86%)	15 / 176 (8.52%)	
occurrences (all)	28	20	

Back pain			
subjects affected / exposed	16 / 177 (9.04%)	17 / 176 (9.66%)	
occurrences (all)	17	21	
Muscle spasms			
subjects affected / exposed	11 / 177 (6.21%)	4 / 176 (2.27%)	
occurrences (all)	14	6	
Pain in extremity			
subjects affected / exposed	15 / 177 (8.47%)	14 / 176 (7.95%)	
occurrences (all)	22	24	
Infections and infestations			
Cystitis			
subjects affected / exposed	7 / 177 (3.95%)	9 / 176 (5.11%)	
occurrences (all)	7	10	
Infection			
subjects affected / exposed	11 / 177 (6.21%)	7 / 176 (3.98%)	
occurrences (all)	14	9	
Nasopharyngitis			
subjects affected / exposed	12 / 177 (6.78%)	17 / 176 (9.66%)	
occurrences (all)	15	20	
Pneumonia			
subjects affected / exposed	9 / 177 (5.08%)	9 / 176 (5.11%)	
occurrences (all)	10	10	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	47 / 177 (26.55%)	38 / 176 (21.59%)	
occurrences (all)	66	60	
Hypokalaemia			
subjects affected / exposed	10 / 177 (5.65%)	4 / 176 (2.27%)	
occurrences (all)	11	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 December 2008	Shorten the treatment-free period between first and second line treatment parts of this study from at least two to at least one week. Justification: The treatment-free period was introduced into the protocol to avoid additive toxicity from both drugs and to provide the patient with time for recreation between the treatment sections of first and second line. However, there can be circumstances that demand a rapid change from first to second line treatment. In those cases a treatment interruption of two weeks is deemed too long. Instead, one week between first and second line treatment is considered to be acceptable also from the pharmacokinetic point-of-view in terms of the elimination half lives of both drugs.
08 June 2010	Change of the statistical design from non-inferiority to superiority due to the results of retrospecitive analyses on sequential therapies with sunitinib and sorafenib. Reduction of number of subjects from 540 to 346, increase of number of centers. Extension of Duration of enrolement. Some other changes according to an updated summary of product characteristics of Nexavar and Sutent.
05 May 2011	Adaption of the protocol according to the current SPC of Sutent® and Nexavar®
19 December 2011	Adaption of the protocol according to the current SPC of Sutent® and Nexavar®
22 March 2012	Adaption of the protocol according to the current SPC of Sutent® and Nexavar®
12 August 2013	Adaption of the protocol according to the current SPC of Sutent® and Nexavar®, calculation of analysis periods and new planned study end.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported