Clinical trial results:
A randomized phase III, double-blind, placebo-controlled, multi-center study to evaluate the efficacy and safety of everolimus (RAD001) in adult patients with advanced hepatocellular carcinoma after failure of sorafenib treatment - the EVOLVE-1 Study

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

Summary

EudraCT number	2009-010196-25
Trial protocol	DE BE AT ES IT FR GR HU
Global end of trial date	15 October 2013

Results information

Result version number	v2 (current)
This version publication date	27 July 2016
First version publication date	13 August 2015
Version creation reason	• Correction of full data set Updated Safety XML is re-loaded

Trial information

Trial identification

Sponsor protocol code	CRAD001O2301

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, +41 613241111, trialandresults.registries@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, +41 613241111, trialandresults.registries@novartis.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	15 October 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 October 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to compare overall survival between the combination treatment of everolimus plus best supportive care (BSC) to placebo plus BSC in patients with advanced hepatocellular carcinoma (HCC) whose disease had progressed while on or after sorafenib treatment or who were intolerant to sorafenib.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	28 April 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 16
Country: Number of subjects enrolled	Austria: 13
Country: Number of subjects enrolled	Belgium: 19
Country: Number of subjects enrolled	Canada: 12
Country: Number of subjects enrolled	China: 13
Country: Number of subjects enrolled	France: 113
Country: Number of subjects enrolled	Germany: 57
Country: Number of subjects enrolled	Greece: 7
Country: Number of subjects enrolled	Hong Kong: 9
Country: Number of subjects enrolled	Hungary: 7
Country: Number of subjects enrolled	Israel: 2
Country: Number of subjects enrolled	Italy: 56
Country: Number of subjects enrolled	Japan: 82
Country: Number of subjects enrolled	Korea, Republic of: 32
Country: Number of subjects enrolled	Spain: 13

Country: Number of subjects enrolled	Taiwan: 26
Country: Number of subjects enrolled	Thailand: 11
Country: Number of subjects enrolled	United States: 58
Worldwide total number of subjects	546
EEA total number of subjects	285

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)	248
From 65 to 84 years	298
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

763 patients screened, 546 randomized. At 14Jun2013 data cut-off (final analysis), 3 pts in everolimus arm, 6 in placebo arm were still on treatment. Of 9 pts, 3 receiving placebo discontinued due to disease progression. Remaining 6 completed study due to sponsor's decision to end study after final results. The LPLV was 15Oct2013.

Pre-assignment

Screening details:

At Screening Visit 1, the Investigator or his/her authorized designee assigned a unique patient number to patients being considered for the study. A screening period of 28 days was allowed to assess eligibility & to start anti-viral prophylaxis for HBV patients.

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Everolimus + Best Supportive Care (BSC)

Arm description:

Patients were assigned to the Everolimus + BSC arm in a ratio of 2:1 over the Placebo arm. Everolimus was taken as a daily oral dose of 7.5 mg but dose adjustments of study drug (reduction, interruption or possible dose re-escalation to starting dose) according to safety findings were allowed. In addition to taking Everolimus, all patients also received BSC as per normal local practice.

Arm type	Experimental
Investigational medicinal product name	Everolimus
Investigational medicinal product code	RAD001
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Everolimus (daily oral dose of 7.5 mg) was formulated as tablets of 2.5 mg strength and blister-packed in units of 10 tablets

Arm title	Placebo + Best Supportive Care

Arm description:

Placebo-Everolimus was taken as a daily oral dose of 7.5 mg and was defined as the control drug. In addition to taking Placebo Everolimus, all patients also received BSC as per normal local practice.

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

Dosage and administration details:

Matching placebo (daily oral dose of 7.5 mg) to the everolimus 2.5 mg tablet strength was blister-packed in units of 10 tablets

Number of subjects in period 1	Everolimus + Best Supportive Care (BSC)	Placebo + Best Supportive Care
Started	362	184
Completed	0	0
Not completed	362	184
Adverse event, serious fatal	13	5
Consent withdrawn by subject	20	7
Adverse event, non-fatal	61	14
New cancer therapy	2	-
Administrative problems	1	1
Sponsor's decision to end study	3	3
Lost to follow-up	1	-
Disease Progression	261	152
Protocol deviation	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Everolimus + Best Supportive Care (BSC)
Reporting group description:	
Patients were assigned to the Everolimus + BSC arm in a ratio of 2:1 over the Placebo arm. Everolimus was taken as a daily oral dose of 7.5 mg but dose adjustments of study drug (reduction, interruption or possible dose re-escalation to starting dose) according to safety findings were allowed. In addition to taking Everolimus, all patients also received BSC as per normal local practice.	
Reporting group title	Placebo + Best Supportive Care
Reporting group description:	
Placebo-Everolimus was taken as a daily oral dose of 7.5 mg and was defined as the control drug. In addition to taking Placebo Everolimus, all patients also received BSC as per normal local practice.	

Reporting group values	Everolimus + Best Supportive Care (BSC)	Placebo + Best Supportive Care	Total
Number of subjects	362	184	546
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	155	93	248
From 65-84 years	207	91	298
85 years and over	0	0	0
Age Continuous | Units: Years			
arithmetic mean	65.1	64.2	
standard deviation	± 11.7	± 10.41	-
Gender, Male/Female Units: Participants			
Female	59	24	83
Male	303	160	463
Age, Customized Units: Subjects			
< 35 years	7	1	8
>=35 - <55 years	48	31	79
>=55 - <65 years	100	61	161
>= 65 years	207	91	298
Race/Ethnicity, Customized Units: Subjects			
Caucasian	192	110	302
Black	6	3	9
Asian	137	58	195
Pacific Islander	0	1	1
Other	27	12	39

End points

End points reporting groups

Reporting group title	Everolimus + Best Supportive Care (BSC)

Reporting group description:

Patients were assigned to the Everolimus + BSC arm in a ratio of 2:1 over the Placebo arm. Everolimus was taken as a daily oral dose of 7.5 mg but dose adjustments of study drug (reduction, interruption or possible dose re-escalation to starting dose) according to safety findings were allowed. In addition to taking Everolimus, all patients also received BSC as per normal local practice.

Reporting group title	Placebo + Best Supportive Care

Reporting group description:

Placebo-Everolimus was taken as a daily oral dose of 7.5 mg and was defined as the control drug. In addition to taking Placebo Everolimus, all patients also received BSC as per normal local practice.

Subject analysis set title	Everolimus 5mg + Best Supportive Care (BSC)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Everolimus was taken as a daily oral dose of 7.5 mg but dose adjustments of study drug (reduction, interruption or possible dose re-escalation to starting dose) according to safety findings were allowed.

Subject analysis set title	Everolimus 7.5mg + Best Supportive Care (BSC)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients were assigned to the Everolimus + BSC arm in a ratio of 2:1 over the Placebo arm. Everolimus was taken as a daily oral dose of 7.5 mg but dose adjustments of study drug (reduction, interruption or possible dose re-escalation to starting dose) according to safety findings were allowed. In addition to taking Everolimus, all patients also received BSC as per normal local practice.

Subject analysis set title	Everolimus 5mg + Best Supportive Care (BSC)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Everolimus was taken as a daily oral dose of 7.5 mg but dose adjustments of study drug (reduction, interruption or possible dose re-escalation to starting dose) according to safety findings were allowed.

Subject analysis set title	Everolimus 7.5mg + Best Supportive Care (BSC)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients were assigned to the Everolimus + BSC arm in a ratio of 2:1 over the Placebo arm. Everolimus was taken as a daily oral dose of 7.5 mg but dose adjustments of study drug (reduction, interruption or possible dose re-escalation to starting dose) according to safety findings were allowed. In addition to taking Everolimus, all patients also received BSC as per normal local practice.

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time from the date of randomization to the date of death from any cause. The comparison of OS between the 2 arms was done using a stratified log-rank test at one-sided 2.5% level of significance.

End point type	Primary

End point timeframe:

When 454 OS events were observed

End point values	Everolimus + Best Supportive Care (BSC)	Placebo + Best Supportive Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	362	184		
Units: Months				
median (confidence interval)	7.56 (6.7 to 8.74)	7.33 (6.28 to 8.74)		

Statistical analyses

Statistical analysis title	Analysis of overall survival
Statistical analysis description: using Kaplan-Meier method and Cox PH model	
Comparison groups	Placebo + Best Supportive Care v Everolimus + Best Supportive Care (BSC)
Number of subjects included in analysis	546
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.675 [1]
Method	Logrank

Notes:

[1] - P-value is obtained from the one-sided log rank test stratified by geographic region and macroscopic vascularinvasion status collected through IVRS.

Secondary: Time to tumor progression (TTP)

End point title	Time to tumor progression (TTP)

End point description:

TTP was defined as the time from the date of randomization to the date of the first documented radiologic confirmation of disease progression. Since the study did not meet the primary objective, TTP was not formally tested.

End point type	Secondary

End point timeframe:

Until all patients have disease progression or leave study due to intolerable adverse events- Estimate of 1 year for each patient

End point values	Everolimus + Best Supportive Care (BSC)	Placebo + Best Supportive Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	362	184		
Units: Months				
median (confidence interval)	2.96 (2.79 to 4.01)	2.6 (1.48 to 2.83)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with disease control rate (DCR)

End point title	Percentage of participants with disease control rate (DCR)

End point description:

DCR is defined as the proportion of participants with a best objective response (BOR) of complete response (CR) or partial response (PR) or stable disease (SD) according to RECIST. The BOR was the best response recorded from the start of the treatment until disease progression. CR is disappearance of all target lesions; PR is at least a 30% decrease in the sum of the longest diameter of all target lesions, taking as reference the baseline sum of the longest diameters; SD is neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for PD. PD is at least a 20% increase in the sum of the longest diameter of all measured target lesions, taking as reference the smallest sum of longest diameter of all target lesions recorded at or after baseline.

End point type	Secondary

End point timeframe:

Until all patients have disease progression or leave study due to intolerable adverse events- Estimate of 1 year for each patient

End point values	Everolimus + Best Supportive Care (BSC)	Placebo + Best Supportive Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	362	184		
Units: Percentage of Participants				
number (not applicable)	56.1	45.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to definitive deterioration of ECOG performance score (PS) score

End point title	Time to definitive deterioration of ECOG performance score (PS) score

End point description:

Change in Eastern Cooperative Oncology Group (ECOG) were assessed by time to definitive performance status deterioration by at least one category on the ECOG scale. Deterioration was considered definitive if no improvement in the ECOG PS was observed at a subsequent measurement. ECOG PS: 0=Fully active, able to carry on all pre-disease performance without restriction, 1=Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; 2=Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours; 3=Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours; 4=Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair; 5=Dead

End point type	Secondary

End point timeframe:

Until all patients have disease progression or leave study due to intolerable adverse events- Estimate of 1 year for each patient.

End point values	Everolimus + Best Supportive Care (BSC)	Placebo + Best Supportive Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	362	184		
Units: Months				
median (confidence interval)	4.27 (3.32 to 4.86)	4.47 (3.02 to 6.08)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to definitive deterioration of EORTC QLQ-C30 scores

End point title	Time to definitive deterioration of EORTC QLQ-C30 scores

End point description:

The primary quality of life endpoint was the time to definitive 5% deterioration from baseline in the global health status/quality of life scale of the EORTC QLQ-C30 questionnaire. Definitive deterioration by at least 5% is defined as a decrease in score by at least 5% compared to baseline, with no later observed increase above this threshold. The EORTC quality of life questionnaire (QLQ) is an integrated system for assessing the healthrelated quality of life (QoL) of cancer patients participating in international clinical trials. All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level. Thus a high score for a functional scale represents a high / healthy level of functioning, a high score for the global health status / QoL represents a high QoL, but a high score for a symptom scale / item represents a high level of symptomatology / problems.

End point type	Secondary

End point timeframe:

Until all patients have disease progression or leave study due to intolerable adverse events - Estimate of 1 year for each patient.

End point values	Everolimus + Best Supportive Care (BSC)	Placebo + Best Supportive Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	362	184		
Units: Months				
median (confidence interval)	2.86 (2.66 to 4.11)	3.45 (2.79 to 4.17)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics assessments - Cmin

End point title	Pharmacokinetics assessments - Cmin

End point description:

Cmin is the pre-dose blood concentration at steady-state (ng/mL). Pre-dose (Cmin) blood samples were collected from all patients in both arms at Visit 3. Steady-state for the Cmin sample was defined as continuous administration of the same dose in the last 4 days prior to the collection of the Cmin sample. Steady-state for the 5 mg every other day regimen was defined as the state when the 5 mg dose was taken 2 days and 4 days before sampling. PK samples were only drawn at visit 3, and only analyzed for patients receiving everolimus at steady state (if patients had received the dose the previous 4 days). In addition summary statistics were only done for each everolimus dose when 3 samples were available. Only valid pre-dose (Cmin) everolimus samples were included in the analysis.

End point type	Secondary

End point timeframe:

Until all patients have disease progression or leave study due to intolerable adverse events - Estimate of 1 year for each patient.

End point values	Everolimus 5mg + Best Supportive Care (BSC)	Everolimus 7.5mg + Best Supportive Care (BSC)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	206		
Units: ng/mL				
arithmetic mean (standard deviation)	9.318 (± 4.9705)	16.141 (± 9.2297)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics assessments - Cmax

End point title	Pharmacokinetics assessments - Cmax

End point description:

Cmax is the maximum (peak) blood drug concentration after dose administration (ng/mL) calculated as the maximum of C1h and C2h. C1h was 1 hour post-dose blood concentration (ng/mL) and C2h was 2 hour post-dose blood concentration (ng/mL). C1h and C2h post-dose samples were collected from all patients in both arms at Visit 3. Steady-state for the C1h and C2h samples was defined as continuous administration of the same dose in the previous 4 days and the day on which the C1h and C2h samples were collected. Steady-state for the 5 mg every other day regimen was defined as the state when the 5 mg dose was taken 2 days and 4 days before sampling. PK samples were only drawn at visit 3, and only analyzed for patients receiving everolimus at steady state (if patients had received the dose the previous 4 days). In addition summary statistics were only done for each everolimus dose when 3 samples were available. Only valid C1h and C2h everolimus samples were included in the analysis.

End point type	Secondary

End point timeframe:

Until all patients have disease progression or leave study due to intolerable adverse events- Estimate of 1 year for each patient.

End point values	Everolimus 5mg + Best Supportive Care (BSC)	Everolimus 7.5mg + Best Supportive Care (BSC)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	229		
Units: ng/mL				
arithmetic mean (standard deviation)	31.592 (± 21.1622)	47.881 (± 21.0999)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Everolimus 7.5mg/d

Reporting group description:

Everolimus 7.5mg/d

Reporting group title	Placebo

Reporting group description:

Placebo

Serious adverse events	Everolimus 7.5mg/d	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	171 / 361 (47.37%)	64 / 182 (35.16%)	
number of deaths (all causes)	47	28	
number of deaths resulting from adverse events	4	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (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	0 / 361 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to peritoneum			

subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic pain			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal carcinoma			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post thrombotic syndrome			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	0 / 361 (0.00%)	2 / 182 (1.10%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular compression			

subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vena cava thrombosis			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (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			
Asthenia			
subjects affected / exposed	9 / 361 (2.49%)	3 / 182 (1.65%)	
occurrences causally related to treatment / all	2 / 9	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	2 / 361 (0.55%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Face oedema			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	5 / 361 (1.39%)	4 / 182 (2.20%)	
occurrences causally related to treatment / all	1 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperpyrexia			

subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	2 / 361 (0.55%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	3 / 361 (0.83%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Non-cardiac chest pain			
subjects affected / exposed	1 / 361 (0.28%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	4 / 361 (1.11%)	2 / 182 (1.10%)	
occurrences causally related to treatment / all	1 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Performance status decreased			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	14 / 361 (3.88%)	2 / 182 (1.10%)	
occurrences causally related to treatment / all	11 / 19	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Immune system disorders			
Allergic oedema			

subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Immobilisation prolonged			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (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			
Testicular swelling			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	2 / 361 (0.55%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 361 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial haemorrhage			
subjects affected / exposed	0 / 361 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchostenosis			

subjects affected / exposed	0 / 361 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	1 / 361 (0.28%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	9 / 361 (2.49%)	4 / 182 (2.20%)	
occurrences causally related to treatment / all	1 / 10	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	9 / 361 (2.49%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	8 / 10	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (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	5 / 361 (1.39%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	5 / 5	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Lung disorder			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infiltration			
subjects affected / exposed	2 / 361 (0.55%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			

subjects affected / exposed	3 / 361 (0.83%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pleurisy			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 361 (0.28%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	5 / 361 (1.39%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	4 / 5	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Productive cough			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (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 / 361 (0.55%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 361 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory arrest			

subjects affected / exposed	0 / 361 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	3 / 361 (0.83%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sleep apnoea syndrome			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract inflammation			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 361 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	2 / 361 (0.55%)	3 / 182 (1.65%)	
occurrences causally related to treatment / all	1 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disorientation			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			

Aspartate aminotransferase increased			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	1 / 361 (0.28%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood uric acid increased			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein abnormal			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac enzymes increased			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical condition abnormal			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	2 / 361 (0.55%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
International normalised ratio increased			

subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin increased			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	2 / 361 (0.55%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count increased			
subjects affected / exposed	0 / 361 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Facial bones fracture			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (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 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand fracture			

subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (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 / 361 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	1 / 361 (0.28%)	2 / 182 (1.10%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (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 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Pyloric stenosis			
subjects affected / exposed	0 / 361 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Atrial fibrillation			
subjects affected / exposed	4 / 361 (1.11%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 361 (0.00%)	2 / 182 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (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	0 / 361 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cardiomyopathy			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			

subjects affected / exposed	0 / 361 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Altered state of consciousness			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amnesia			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebellar haemorrhage			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (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 / 361 (0.55%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	0 / 361 (0.00%)	2 / 182 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cognitive disorder			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia			

subjects affected / exposed	0 / 361 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			
subjects affected / exposed	0 / 361 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic hyperosmolar coma			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysarthria			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (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	2 / 361 (0.55%)	2 / 182 (1.10%)	
occurrences causally related to treatment / all	0 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	0 / 361 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hemiplegia			
subjects affected / exposed	2 / 361 (0.55%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatic encephalopathy			

subjects affected / exposed	5 / 361 (1.39%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic encephalopathy			
subjects affected / exposed	0 / 361 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorder			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral motor neuropathy			
subjects affected / exposed	0 / 361 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	0 / 361 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	14 / 361 (3.88%)	3 / 182 (1.65%)	
occurrences causally related to treatment / all	12 / 18	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	0 / 361 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			

subjects affected / exposed	2 / 361 (0.55%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	3 / 361 (0.83%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	4 / 361 (1.11%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	5 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	0 / 361 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ocular icterus			
subjects affected / exposed	0 / 361 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	0 / 361 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	9 / 361 (2.49%)	8 / 182 (4.40%)	
occurrences causally related to treatment / all	1 / 13	1 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			

subjects affected / exposed	4 / 361 (1.11%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	13 / 361 (3.60%)	11 / 182 (6.04%)	
occurrences causally related to treatment / all	2 / 14	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ischaemic			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic obstruction			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (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 / 361 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (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	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faeces discoloured			

subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric antral vascular ectasia			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	0 / 361 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	5 / 361 (1.39%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	2 / 6	1 / 1	
deaths causally related to treatment / all	0 / 1	1 / 1	
Haematemesis			
subjects affected / exposed	1 / 361 (0.28%)	2 / 182 (1.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileal ulcer			
subjects affected / exposed	0 / 361 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			

subjects affected / exposed	2 / 361 (0.55%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal haemorrhage			
subjects affected / exposed	0 / 361 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 361 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	0 / 361 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth ulceration			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal haemorrhage			
subjects affected / exposed	0 / 361 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal varices haemorrhage			
subjects affected / exposed	1 / 361 (0.28%)	3 / 182 (1.65%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal haemorrhage			
subjects affected / exposed	0 / 361 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal haemorrhage			

subjects affected / exposed	0 / 361 (0.00%)	1 / 182 (0.55%)	
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 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	3 / 361 (0.83%)	2 / 182 (1.10%)	
occurrences causally related to treatment / all	2 / 3	1 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Varices oesophageal			
subjects affected / exposed	0 / 361 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 361 (0.55%)	3 / 182 (1.65%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	0 / 361 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stenosis			
subjects affected / exposed	1 / 361 (0.28%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			

subjects affected / exposed	2 / 361 (0.55%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	2 / 361 (0.55%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cirrhosis alcoholic			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cirrhosis			
subjects affected / exposed	8 / 361 (2.22%)	3 / 182 (1.65%)	
occurrences causally related to treatment / all	2 / 8	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	5 / 361 (1.39%)	4 / 182 (2.20%)	
occurrences causally related to treatment / all	1 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic pain			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatorenal syndrome			
subjects affected / exposed	1 / 361 (0.28%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	5 / 361 (1.39%)	5 / 182 (2.75%)	
occurrences causally related to treatment / all	2 / 5	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			

subjects affected / exposed	1 / 361 (0.28%)	2 / 182 (1.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			
subjects affected / exposed	1 / 361 (0.28%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pruritus			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Anuria			
subjects affected / exposed	2 / 361 (0.55%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haematuria			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal disorder			

subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (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	11 / 361 (3.05%)	2 / 182 (1.10%)	
occurrences causally related to treatment / all	2 / 11	1 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal failure acute			
subjects affected / exposed	8 / 361 (2.22%)	2 / 182 (1.10%)	
occurrences causally related to treatment / all	2 / 8	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure chronic			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 361 (0.55%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mobility decreased			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			

subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (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 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Atypical pneumonia			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	2 / 361 (0.55%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial toxaemia			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Candidiasis			

subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis suppurative			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Citrobacter infection			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue fever			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	2 / 361 (0.55%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis bacterial			

subjects affected / exposed	0 / 361 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 361 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Listeriosis			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Morganella infection			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	4 / 361 (1.11%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pneumocystis jiroveci pneumonia			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	18 / 361 (4.99%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	8 / 19	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Sepsis			

subjects affected / exposed	6 / 361 (1.66%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	3 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 361 (0.28%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	1 / 361 (0.28%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	8 / 361 (2.22%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	5 / 9	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 361 (0.28%)	2 / 182 (1.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	2 / 361 (0.55%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			

subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperammonaemia			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	2 / 361 (0.55%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercholesterolaemia			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 361 (0.28%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	2 / 361 (0.55%)	3 / 182 (1.65%)	
occurrences causally related to treatment / all	2 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	2 / 361 (0.55%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 361 (0.28%)	0 / 182 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			

subjects affected / exposed	6 / 361 (1.66%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	1 / 7	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	0 / 361 (0.00%)	1 / 182 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Everolimus 7.5mg/d	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	343 / 361 (95.01%)	147 / 182 (80.77%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	11 / 361 (3.05%)	11 / 182 (6.04%)	
occurrences (all)	11	12	
Aspartate aminotransferase increased			
subjects affected / exposed	23 / 361 (6.37%)	19 / 182 (10.44%)	
occurrences (all)	25	21	
Gamma-glutamyltransferase increased			
subjects affected / exposed	18 / 361 (4.99%)	12 / 182 (6.59%)	
occurrences (all)	19	12	
Platelet count decreased			
subjects affected / exposed	21 / 361 (5.82%)	0 / 182 (0.00%)	
occurrences (all)	25	0	
Weight decreased			
subjects affected / exposed	34 / 361 (9.42%)	8 / 182 (4.40%)	
occurrences (all)	35	8	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	31 / 361 (8.59%)	4 / 182 (2.20%)	
occurrences (all)	32	4	
Headache			

subjects affected / exposed	26 / 361 (7.20%)	9 / 182 (4.95%)	
occurrences (all)	31	10	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	56 / 361 (15.51%)	13 / 182 (7.14%)	
occurrences (all)	67	14	
Thrombocytopenia			
subjects affected / exposed	40 / 361 (11.08%)	2 / 182 (1.10%)	
occurrences (all)	48	2	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	59 / 361 (16.34%)	31 / 182 (17.03%)	
occurrences (all)	63	36	
Fatigue			
subjects affected / exposed	90 / 361 (24.93%)	30 / 182 (16.48%)	
occurrences (all)	97	32	
Oedema peripheral			
subjects affected / exposed	100 / 361 (27.70%)	25 / 182 (13.74%)	
occurrences (all)	112	29	
Pyrexia			
subjects affected / exposed	86 / 361 (23.82%)	13 / 182 (7.14%)	
occurrences (all)	119	16	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	54 / 361 (14.96%)	27 / 182 (14.84%)	
occurrences (all)	64	30	
Abdominal pain upper			
subjects affected / exposed	28 / 361 (7.76%)	17 / 182 (9.34%)	
occurrences (all)	31	21	
Ascites			
subjects affected / exposed	51 / 361 (14.13%)	23 / 182 (12.64%)	
occurrences (all)	55	24	
Constipation			
subjects affected / exposed	31 / 361 (8.59%)	23 / 182 (12.64%)	
occurrences (all)	33	25	
Diarrhoea			

subjects affected / exposed	94 / 361 (26.04%)	25 / 182 (13.74%)	
occurrences (all)	118	27	
Dry mouth			
subjects affected / exposed	23 / 361 (6.37%)	5 / 182 (2.75%)	
occurrences (all)	23	5	
Nausea			
subjects affected / exposed	60 / 361 (16.62%)	25 / 182 (13.74%)	
occurrences (all)	70	30	
Stomatitis			
subjects affected / exposed	142 / 361 (39.34%)	9 / 182 (4.95%)	
occurrences (all)	186	9	
Vomiting			
subjects affected / exposed	55 / 361 (15.24%)	17 / 182 (9.34%)	
occurrences (all)	68	17	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	79 / 361 (21.88%)	23 / 182 (12.64%)	
occurrences (all)	85	24	
Dyspnoea			
subjects affected / exposed	45 / 361 (12.47%)	21 / 182 (11.54%)	
occurrences (all)	51	23	
Epistaxis			
subjects affected / exposed	78 / 361 (21.61%)	5 / 182 (2.75%)	
occurrences (all)	92	5	
Pleural effusion			
subjects affected / exposed	19 / 361 (5.26%)	3 / 182 (1.65%)	
occurrences (all)	19	3	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	24 / 361 (6.65%)	6 / 182 (3.30%)	
occurrences (all)	24	6	
Pruritus			
subjects affected / exposed	64 / 361 (17.73%)	29 / 182 (15.93%)	
occurrences (all)	76	32	
Rash			

subjects affected / exposed	76 / 361 (21.05%)	16 / 182 (8.79%)	
occurrences (all)	89	16	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	37 / 361 (10.25%)	15 / 182 (8.24%)	
occurrences (all)	40	15	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	24 / 361 (6.65%)	13 / 182 (7.14%)	
occurrences (all)	25	17	
Pain in extremity			
subjects affected / exposed	19 / 361 (5.26%)	9 / 182 (4.95%)	
occurrences (all)	22	9	
Infections and infestations			
Hepatitis B			
subjects affected / exposed	25 / 361 (6.93%)	8 / 182 (4.40%)	
occurrences (all)	27	8	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	114 / 361 (31.58%)	27 / 182 (14.84%)	
occurrences (all)	133	29	
Hyperglycaemia			
subjects affected / exposed	20 / 361 (5.54%)	3 / 182 (1.65%)	
occurrences (all)	31	3	
Hypokalaemia			
subjects affected / exposed	19 / 361 (5.26%)	1 / 182 (0.55%)	
occurrences (all)	24	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 June 2010	treatment duration with sorafenib was specified as 8 weeks.
03 December 2010	Inclusion/Exclusion modified.

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.

Three patients (1 in the everolimus arm and 2 in the placebo arm were excluded from the Safety Set. These three patients were randomized but never received any study treatment.

Notes: