



Clinical trial results:

RAMSETE: A single arm, multicenter, single-stage phase II trial of RAD001 in Advanced and Metastatic Silent neuro-Endocrine Tumors in Europe

Summary

EudraCT number	2008-006182-88
Trial protocol	SE DE GB ES NL IT
Global end of trial date	07 November 2016

Results information

Result version number	v1 (current)
This version publication date	22 November 2017
First version publication date	22 November 2017

Trial information

Trial identification

Sponsor protocol code	CRAD001CDE16
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00688623
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, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@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	07 November 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 November 2016
Global end of trial reached?	Yes
Global end of trial date	07 November 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to evaluate the efficacy of everolimus as monotherapy in patients with non-syndromic NETs. Efficacy is defined as the proportion of patients with a complete (CR) or partial response (PR) according to RECIST criteria

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	24 June 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	Germany: 19
Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Spain: 15
Country: Number of subjects enrolled	Sweden: 4
Country: Number of subjects enrolled	Netherlands: 6
Country: Number of subjects enrolled	United Kingdom: 16
Worldwide total number of subjects	73
EEA total number of subjects	73

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	44
From 65 to 84 years	29
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Eight-two patients were screened and 73 were treated with study drug.

Period 1

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

Arms

Arm title	Everolimus
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Arm description:

10 mg/day dose of everolimus was given by continuous oral daily dosing of two 5 mg tablets

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:

two 5 mg tablets of everolimus orally once daily

Number of subjects in period 1	Everolimus
Started	73
Safety analysis set	73
Per protocol (PP)	60
Completed	18
Not completed	55
Adverse event, serious fatal	3
Consent withdrawn by subject	4
Adverse event, non-fatal	22
disease progression	23
abnormal lab value	1
Protocol deviation	2

Baseline characteristics

Reporting groups

Reporting group title	Everolimus
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Reporting group description:

10 mg/day dose of everolimus was given by continuous oral daily dosing of two 5 mg tablets

Reporting group values	Everolimus	Total	
Number of subjects	73	73	
Age categorical			
Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age Continuous			
Units: years			
arithmetic mean	59.9		
standard deviation	± 13.0	-	
Gender, Male/Female			
Units: Subjects			
Female	33	33	
Male	40	40	
Tumor histology/cytology			
Units: Subjects			
Bronchial (thymic) carcinoid -typical	9	9	
Bronchial (thymic) carcinoid - atypical	12	12	
Neuroendocrine tumor	16	16	
Neuroendocrine carcinoma	36	36	
Time since first diagnosis			
Units: Subjects			
< 1 year	19	19	
1 year to < 3 years	26	26	
3 years to < 6 years	17	17	
6 years to < 10 years	3	3	
≥ 10 years	6	6	
Missing	2	2	
Race/Ethnicity, Customized			
Units: Subjects			
Caucasian	71	71	
Other	2	2	

End points

End points reporting groups

Reporting group title	Everolimus
Reporting group description: 10 mg/day dose of everolimus was given by continuous oral daily dosing of two 5 mg tablets	

Primary: Percentage of participants' Best Overall Response Rate - Per Protocol Set (PP)

End point title	Percentage of participants' Best Overall Response Rate - Per Protocol Set (PP) ^[1]
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End point description:

Overall response rate (ORR) was based on RECIST central assessment and defined as the percentage of patients with best overall response (BOR) of a confirmed complete response (CR) or partial response (PR). The BOR was calculated on basis of the tumor or overall lesion response evaluated at each visit. To be assigned a status of PR or CR, changes in tumor measurements had to be confirmed by repeat assessments obtained within 4 weeks after the criteria for response were first met. Assessments was based on RECIST criteria 1.0. Measurable disease lesions had to be accurately measured in at least one dimension with longest diameter ≥ 20 mm using conventional techniques or ≥ 10 mm with spiral CT scan (with minimum lesion size no less than double the slice thickness). PR required 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. CR required disappearance of all target and non-target lesions.

End point type	Primary
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End point timeframe:

baseline up to approximately 24 months

Notes:

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

Justification: No statistical analysis was done.

End point values	Everolimus			
Subject group type	Reporting group			
Number of subjects analysed	60			
Units: percentage of participants				
number (not applicable)				
Complete response (CR)	0.0			
Partial response	0.0			
Stable disease (SD)	56.7			
Progressive disease (PD)	43.3			
Unknown	0.0			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of participants with Objective Response Rate - Per Protocol Set (PP)

End point title	Percentage of participants with Objective Response Rate - Per Protocol Set (PP) ^[2]
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End point description:

Overall Response Rate (ORR) was calculated for total PP population based on central review as confirmatory, primary analysis as well as for ITT population as sensitivity analysis. It was presented with relative frequencies and the exact 2-sided 80% confidence limit (CL; computed using the Clopper-Pearson method). If the lower limit of the CI did not include $p_0=5\%$, the hypothesis that $p \leq 5\%$ was rejected. The primary analysis was based on the PP Set

End point type	Primary
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End point timeframe:

baseline up to approximately 12 months

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was done.

End point values	Everolimus			
Subject group type	Reporting group			
Number of subjects analysed	60			
Units: percentage of participants				
number (confidence interval 80%)	0.0 (0.0 to 3.8)			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of participants with a Overall Response Rate with a complete response (CR) or partial response (PR) ITT set

End point title	Percentage of participants with a Overall Response Rate with a complete response (CR) or partial response (PR) ITT set ^[3]
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End point description:

The best overall response (BOR) was calculated on basis of the tumor of overall lesion response evaluated at each visit. To be assigned a status of PR or CR, changes in tumor measurements had to be confirmed by repeat assessments that should have been performed not less than 4 weeks after the criteria for response were first met. Assessments was based on RECIST criteria 1.0. Measurable disease lesions had to be accurately measured in at least one dimension with longest diameter ≥ 20 mm using conventional techniques or ≥ 10 mm with spiral CT scan (with minimum lesion size no less than double the slice thickness). PR required 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. CR required disappearance of all target and non-target lesions.

End point type	Primary
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End point timeframe:

baseline up to approximately 12 months

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was done.

End point values	Everolimus			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: percentage of participants				
number (not applicable)				
Complete response (CR)	0.0			
Partial response	0.0			

Stable disease (SD)	74.0			
Progressive disease (PD)	16.4			
Unknown	9.6			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of participants with Objective Response Rate - ITT Set

End point title	Percentage of participants with Objective Response Rate - ITT Set ^[4]
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End point description:

Overall Response Rate (ORR) was presented for ITT population as sensitivity analysis. It was presented with relative frequencies and the exact 2-sided 80% confidence limit (CL; computed using the Clopper-Pearson method). If the lower limit of the CI did not include $p_0=5\%$, the hypothesis that $p \leq 5\%$ was rejected.

End point type	Primary
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End point timeframe:

baseline up to approximately 12 months

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was done.

End point values	Everolimus			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: percentage of participants				
number (confidence interval 80%)	0.0 (0.0 to 3.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with Disease Control Rate (DCR) for Per Protocol (PP) and ITT sets

End point title	Percentage of participants with Disease Control Rate (DCR) for Per Protocol (PP) and ITT sets
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End point description:

DCR was based on central radiologic review and is defined as the percentage of patients with a best overall response of 'Complete response' (CR), 'Partial response' (PR) or 'Stable disease' (SD). Relative frequencies together with their exact 2-sided 80% confidence intervals were presented

End point type	Secondary
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End point timeframe:

baseline up to approximately 12 months

End point values	Everolimus			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: percentage of participants				
number (confidence interval 80%)				
DCR for Per protocol set (60)	56.7 (47.6 to 65.4)			
DCR for Intent to treat set (73)	50.7 (42.6 to 58.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants' biochemical response rate based on the tumor marker Chromogranin A (CgA)

End point title	Percentage of participants' biochemical response rate based on the tumor marker Chromogranin A (CgA)
End point description: Biochemical response was defined as level and change from baseline in CgA during the course of the trial. The resulting values showed a high variation and were not interpretable, as different methodology was used for the assessment of CgA at the individual centers.	
End point type	Secondary
End point timeframe: baseline up to approximately 12 months	

End point values	Everolimus			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[5]			
Units: percentage of participants				

Notes:

[5] - Values had high variation, were not interpretable; methods for assessing CgA differed across centers

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Progression Free Survival (PFS) for Per Protocol (PP) and ITT sets

End point title	Duration of Progression Free Survival (PFS) for Per Protocol (PP) and ITT sets
End point description: Duration of PFS was defined as the time from first study drug administration to objective tumor progression or death from any cause. Observations from patients not experiencing tumor progression or death at date of DBC were censored with the date of their last adequate tumor assessment	
End point type	Secondary
End point timeframe: baseline up to approximately 12 months	

End point values	Everolimus			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: days				
median (confidence interval 95%)				
PFS days for Per protocol set (60)	185 (160 to 262)			
PFS days for Intent to treat set (73)	190 (161 to 262)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) for Per Protocol (PP) and ITT sets

End point title	Overall Survival (OS) for Per Protocol (PP) and ITT sets
End point description:	
OS was defined as the time from first study drug administration to death from any cause. If a patient was not known to have died at date of database closure, overall survival was censored at the date of last contact.	
End point type	Secondary
End point timeframe:	
baseline up to approximately 12 months	

End point values	Everolimus			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: days				
arithmetic mean (standard error)				
OS for Per protocol set (60)	451.8 (± 19.8)			
OS for Intent to treat set (73)	437.1 (± 18.6)			

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 are reported in this record from 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
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Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Everolimus
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Reporting group description:

Everolimus

Serious adverse events	Everolimus		
Total subjects affected by serious adverse events			
subjects affected / exposed	48 / 73 (65.75%)		
number of deaths (all causes)	5		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to central nervous system			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Aortic rupture			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Circulatory collapse			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Hypotension			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lymphoedema			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Astringent therapy			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fatigue			
subjects affected / exposed	2 / 73 (2.74%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oedema			
subjects affected / exposed	3 / 73 (4.11%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Oedema peripheral			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Pyrexia			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Sudden death			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	4 / 73 (5.48%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	1 / 1		
Lung infiltration			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonitis			

subjects affected / exposed	2 / 73 (2.74%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	2 / 73 (2.74%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Restlessness			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 73 (4.11%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 73 (4.11%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Blood potassium decreased subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Haemoglobin decreased			
subjects affected / exposed	2 / 73 (2.74%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Expired product administered			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Toxicity to various agents			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atrioventricular block			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			

subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Palpitations			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tachycardia			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Presyncope			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lymphatic obstruction			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Retinal detachment			

subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 73 (2.74%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Ascites			
subjects affected / exposed	2 / 73 (2.74%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	2 / 73 (2.74%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	5 / 73 (6.85%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Enteritis			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Flatulence			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal obstruction			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			

subjects affected / exposed	3 / 73 (4.11%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Intestinal perforation			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Melaena			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Subileus			
subjects affected / exposed	2 / 73 (2.74%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	2 / 73 (2.74%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholangitis			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Incontinence			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Adrenocortical insufficiency acute			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	3 / 73 (4.11%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Bone pain			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal pain			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Infections and infestations Febrile infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 73 (1.37%) 0 / 1 0 / 0		
Gastroenteritis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 73 (1.37%) 0 / 1 0 / 0		
Gastroenteritis viral subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 73 (1.37%) 0 / 1 0 / 0		
Gastrointestinal infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	2 / 73 (2.74%) 0 / 2 0 / 0		
H1N1 influenza subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 73 (1.37%) 0 / 1 0 / 0		
Herpes zoster subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 73 (1.37%) 2 / 2 0 / 0		
Liver abscess subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 73 (1.37%) 1 / 1 0 / 0		
Lung abscess subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 73 (1.37%) 0 / 1 0 / 0		
Lymphangitis			

subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	5 / 73 (6.85%)		
occurrences causally related to treatment / all	2 / 6		
deaths causally related to treatment / all	1 / 1		
Pseudomonas infection			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis acute			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Subdiaphragmatic abscess			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 73 (2.74%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Diabetes mellitus			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			

subjects affected / exposed	2 / 73 (2.74%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Everolimus		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	72 / 73 (98.63%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	4 / 73 (5.48%)		
occurrences (all)	6		
Vascular disorders			
Flushing			
subjects affected / exposed	4 / 73 (5.48%)		
occurrences (all)	4		
Hypertension			
subjects affected / exposed	5 / 73 (6.85%)		
occurrences (all)	8		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	19 / 73 (26.03%)		
occurrences (all)	32		
Chest pain			
subjects affected / exposed	8 / 73 (10.96%)		
occurrences (all)	9		
Chills			
subjects affected / exposed	5 / 73 (6.85%)		
occurrences (all)	6		
Fatigue			
subjects affected / exposed	19 / 73 (26.03%)		
occurrences (all)	21		
Mucosal inflammation			

subjects affected / exposed	18 / 73 (24.66%)		
occurrences (all)	33		
Oedema			
subjects affected / exposed	5 / 73 (6.85%)		
occurrences (all)	5		
Oedema peripheral			
subjects affected / exposed	15 / 73 (20.55%)		
occurrences (all)	21		
Pain			
subjects affected / exposed	5 / 73 (6.85%)		
occurrences (all)	5		
Pyrexia			
subjects affected / exposed	11 / 73 (15.07%)		
occurrences (all)	16		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	23 / 73 (31.51%)		
occurrences (all)	34		
Dyspnoea			
subjects affected / exposed	18 / 73 (24.66%)		
occurrences (all)	21		
Epistaxis			
subjects affected / exposed	10 / 73 (13.70%)		
occurrences (all)	12		
Oropharyngeal pain			
subjects affected / exposed	7 / 73 (9.59%)		
occurrences (all)	9		
Pneumonitis			
subjects affected / exposed	7 / 73 (9.59%)		
occurrences (all)	8		
Psychiatric disorders			
Depression			
subjects affected / exposed	4 / 73 (5.48%)		
occurrences (all)	5		
Insomnia			

subjects affected / exposed	7 / 73 (9.59%)		
occurrences (all)	7		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	5 / 73 (6.85%)		
occurrences (all)	9		
Aspartate aminotransferase increased			
subjects affected / exposed	5 / 73 (6.85%)		
occurrences (all)	9		
Blood alkaline phosphatase increased			
subjects affected / exposed	7 / 73 (9.59%)		
occurrences (all)	7		
Blood glucose increased			
subjects affected / exposed	5 / 73 (6.85%)		
occurrences (all)	5		
Blood lactate dehydrogenase increased			
subjects affected / exposed	5 / 73 (6.85%)		
occurrences (all)	5		
Blood potassium decreased			
subjects affected / exposed	5 / 73 (6.85%)		
occurrences (all)	5		
Blood thyroid stimulating hormone decreased			
subjects affected / exposed	5 / 73 (6.85%)		
occurrences (all)	5		
Blood triglycerides increased			
subjects affected / exposed	4 / 73 (5.48%)		
occurrences (all)	5		
Gamma-glutamyltransferase increased			
subjects affected / exposed	8 / 73 (10.96%)		
occurrences (all)	8		
Haemoglobin decreased			
subjects affected / exposed	5 / 73 (6.85%)		
occurrences (all)	8		
Neutrophil count decreased			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Platelet count decreased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Weight decreased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>White blood cell count decreased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>4 / 73 (5.48%)</p> <p>7</p> <p>6 / 73 (8.22%)</p> <p>10</p> <p>17 / 73 (23.29%)</p> <p>18</p> <p>4 / 73 (5.48%)</p> <p>14</p>		
<p>Cardiac disorders</p> <p>Tachycardia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>7 / 73 (9.59%)</p> <p>7</p>		
<p>Nervous system disorders</p> <p>Dizziness</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dysgeusia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Headache</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Lethargy</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>5 / 73 (6.85%)</p> <p>5</p> <p>7 / 73 (9.59%)</p> <p>7</p> <p>10 / 73 (13.70%)</p> <p>14</p> <p>8 / 73 (10.96%)</p> <p>12</p>		
<p>Blood and lymphatic system disorders</p> <p>Anaemia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>11 / 73 (15.07%)</p> <p>13</p>		
<p>Gastrointestinal disorders</p> <p>Abdominal pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Abdominal pain upper</p>	<p>18 / 73 (24.66%)</p> <p>22</p>		

subjects affected / exposed	9 / 73 (12.33%)		
occurrences (all)	13		
Aphthous ulcer			
subjects affected / exposed	4 / 73 (5.48%)		
occurrences (all)	5		
Constipation			
subjects affected / exposed	9 / 73 (12.33%)		
occurrences (all)	11		
Diarrhoea			
subjects affected / exposed	30 / 73 (41.10%)		
occurrences (all)	57		
Dry mouth			
subjects affected / exposed	4 / 73 (5.48%)		
occurrences (all)	4		
Flatulence			
subjects affected / exposed	4 / 73 (5.48%)		
occurrences (all)	5		
Mouth ulceration			
subjects affected / exposed	12 / 73 (16.44%)		
occurrences (all)	14		
Nausea			
subjects affected / exposed	22 / 73 (30.14%)		
occurrences (all)	28		
Stomatitis			
subjects affected / exposed	15 / 73 (20.55%)		
occurrences (all)	32		
Vomiting			
subjects affected / exposed	18 / 73 (24.66%)		
occurrences (all)	25		
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	7 / 73 (9.59%)		
occurrences (all)	10		
Onychoclasia			
subjects affected / exposed	7 / 73 (9.59%)		
occurrences (all)	7		

Pruritus			
subjects affected / exposed	8 / 73 (10.96%)		
occurrences (all)	9		
Rash			
subjects affected / exposed	32 / 73 (43.84%)		
occurrences (all)	47		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 73 (9.59%)		
occurrences (all)	11		
Back pain			
subjects affected / exposed	12 / 73 (16.44%)		
occurrences (all)	16		
Flank pain			
subjects affected / exposed	4 / 73 (5.48%)		
occurrences (all)	4		
Musculoskeletal pain			
subjects affected / exposed	4 / 73 (5.48%)		
occurrences (all)	4		
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	4 / 73 (5.48%)		
occurrences (all)	5		
Cystitis			
subjects affected / exposed	5 / 73 (6.85%)		
occurrences (all)	7		
Nasopharyngitis			
subjects affected / exposed	8 / 73 (10.96%)		
occurrences (all)	15		
Pneumonia			
subjects affected / exposed	5 / 73 (6.85%)		
occurrences (all)	5		
Respiratory tract infection			
subjects affected / exposed	4 / 73 (5.48%)		
occurrences (all)	4		
Urinary tract infection			

subjects affected / exposed	11 / 73 (15.07%)		
occurrences (all)	14		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	23 / 73 (31.51%)		
occurrences (all)	29		
Hypercholesterolaemia			
subjects affected / exposed	12 / 73 (16.44%)		
occurrences (all)	15		
Hyperglycaemia			
subjects affected / exposed	6 / 73 (8.22%)		
occurrences (all)	7		
Hypertriglyceridaemia			
subjects affected / exposed	8 / 73 (10.96%)		
occurrences (all)	14		
Hypokalaemia			
subjects affected / exposed	9 / 73 (12.33%)		
occurrences (all)	12		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 April 2010	Protocol was updated to include new background information. Addition of guidelines for management of hepatitis B and C and management of hyperglycemia and guidance on the usage of CYP3A4 and/or P-glycoprotein (PgP) inducers and inhibitors was modified. Entry criteria was clarified. Change in ECOG status table from grade 0-3 to grade 0-5 was made.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported