Clinical trial results:
A randomized, double-blind, placebo-controlled study of RAD0001 in the treatment of Angiomyolipoma in patients with either Tuberous Sclerosis Complex (TSC) or Sporadic Lymphangioleiomyomatosis (LAM)

Due to EudraCT system limitations, which EMA is aware of, results of crossover studies and data using 999 as data points are not accurately represented in this record. Please go to https://www.novctrd.com/CtrdWeb/home.nov for complete trial results

Summary

EudraCT number	2008-002113-48
Trial protocol	DE FR NL GB IT ES
Global end of trial date	06 November 2015

Results information

Result version number	v1 (current)
This version publication date	19 July 2018
First version publication date	19 July 2018

Trial information

Trial identification

Sponsor protocol code	CRAD001M2302

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00790400
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,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,

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	06 November 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 November 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of Study CRAD001M2302 was to compare the angiomyolipoma response rate of everolimus versus placebo in patients with angiomyolipomata associated with either TSC or sporadic LAM.

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 2009
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	Canada: 5
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Germany: 27
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Japan: 10
Country: Number of subjects enrolled	Netherlands: 13
Country: Number of subjects enrolled	Poland: 5
Country: Number of subjects enrolled	Russian Federation: 8
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	United States: 32
Worldwide total number of subjects	118
EEA total number of subjects	63

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)	118
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A multicenter trial conducted at 24 sites in 11 countries. As the primary analysis of the core phase of the study favored everolimus over placebo, an open-label extension phase started: patients randomized in placebo were offered to switch on everolimus and those still receiving everolimus at the end of the core phase could continue the treatment.

Pre-assignment

Screening details:

The trial had a 2:1 randomization in favor of the everolimus arm. 118 patients were randomized to the core phase of the study. 112 patients received everolimus during core and/or extension phase.

Period 1

Period 1 title	Double-blind Period (Core phase)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Everolimus

Arm description:

Study drug 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:

Everolimus is used in 5 mg strength tablets, blister-packed under aluminum foil in units of ten tablets and dosed on a daily basis. It was given by continuous oral daily dosing of two 5 mg tablets.

Arm title	Placebo

Arm description:

Placebo was given by continuous oral daily dosing of two 5 mg tablets.

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

Dosage and administration details:

Everolimus Placebo, similar to the Everolimus, was used in 5 mg strength tablets, blister-packed under aluminum foil in units of ten tablets and dosed on a daily basis. It was given by continuous oral daily dosing of two 5 mg tablets.

Number of subjects in period 1	Everolimus	Placebo
Started	79	39
Completed	72	26
Not completed	7	13
Adverse event, serious fatal	1	-
Consent withdrawn by subject	1	-
Adverse event, non-fatal	2	4
Administrative problems	1	-
Progressive disease	-	9
Abnormal lab value (s)	1	-
Protocol deviation	1	-

Period 2

Period 2 title	Everolimus Period (Core or Extension)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Everolimus

Arm description:

Study drug 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:

Everolimus is used in 5 mg strength tablets, blister-packed under aluminum foil in units of ten tablets and dosed on a daily basis. It was given by continuous oral daily dosing of two 5 mg tablets.
tablets.

Number of subjects in period 2[1][2]	Everolimus
Started	72
Completed	83
Not completed	29
Adverse event, serious fatal	1
Consent withdrawn by subject	7

Disease progression	5
Adverse event, non-fatal	9
Administrative problems	2
New treatment	2
Lost to follow-up	1
Abnormal lab value (s)	1
Protocol deviation	1
Joined	40
Dropped off the study	7
Transferred in from other group/arm	33

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Period 1 was for everolimus & placebo. Period 2 was for anyone who had at least 1 dose of everolimus either in period 1 (started = those on everolimus who completed period 1 & moved to period 2) or in period 2, which contains those who were on placebo in period 1 and switched to everolimus in period 2.
[2] - The number of subjects transferring in and out of the arms in the period are not the same. It is expected the net number of transfers in and out of the arms in a period, will be zero.
Justification: This period includes all the subjects from period 1 who took everolimus plus any other subject who took at least 1 dose of everolimus throughout the duration of the study.

Baseline characteristics

Reporting groups	
Reporting group title	Everolimus
Reporting group description:	
Study drug was given by continuous oral daily dosing of two 5 mg tablets.	
Reporting group title	Placebo
Reporting group description:	
Placebo was given by continuous oral daily dosing of two 5 mg tablets.	

Reporting group values	Everolimus	Placebo	Total
Number of subjects	79	39	118
Age Categorical Units: Subjects			
<30 years	35	20	55
≥ 30 years	44	19	63
Age Continuous Units: years			
arithmetic mean	32.5	31	
standard deviation	± 10.37	± 9.64	-
Gender, Male/Female Units: Subjects			
Female	52	26	78
Male	27	13	40

Subject analysis sets	
Subject analysis set title	Everolimus randomized (Core period)
Subject analysis set type	Full analysis
Subject analysis set description:	
Study drug was given by continuous oral daily dosing of two 5 mg tablets.	
Subject analysis set title	Placebo randomized (Core period)
Subject analysis set type	Full analysis
Subject analysis set description:	
Placebo was given by continuous oral daily dosing of two 5 mg tablets.	
Subject analysis set title	Everolimus (Core and/or Extension period)
Subject analysis set type	Full analysis
Subject analysis set description:	
Patients initially randomized in everolimus and patients initially randomized in placebo but who crossed-over to everolimus during extension.	

Reporting group values	Everolimus randomized (Core period)	Placebo randomized (Core period)	Everolimus (Core and/or Extension period)
Number of subjects	79	39	112
Age Categorical Units: Subjects			
<30 years	35	20	49
≥ 30 years	44	19	63

Age Continuous Units: years			
arithmetic mean	32.5	31	33.18
standard deviation	± 10.37	± 9.64	± 10.287
Gender, Male/Female Units: Subjects			
Female	52	26	73
Male	27	13	39

End points

End points reporting groups

Reporting group title	Everolimus
Reporting group description:	
Study drug was given by continuous oral daily dosing of two 5 mg tablets.	
Reporting group title	Placebo
Reporting group description:	
Placebo was given by continuous oral daily dosing of two 5 mg tablets.	
Reporting group title	Everolimus
Reporting group description:	
Study drug was given by continuous oral daily dosing of two 5 mg tablets.	
Subject analysis set title	Everolimus randomized (Core period)
Subject analysis set type	Full analysis
Subject analysis set description:	
Study drug was given by continuous oral daily dosing of two 5 mg tablets.	
Subject analysis set title	Placebo randomized (Core period)
Subject analysis set type	Full analysis
Subject analysis set description:	
Placebo was given by continuous oral daily dosing of two 5 mg tablets.	
Subject analysis set title	Everolimus (Core and/or Extension period)
Subject analysis set type	Full analysis
Subject analysis set description:	
Patients initially randomized in everolimus and patients initially randomized in placebo but who crossed-over to everolimus during extension.	

Primary: Angiomyolipoma response rate as Per Central Radiology Review

End point title	Angiomyolipoma response rate as Per Central Radiology Review
End point description:	
Angiomyolipoma response defined as the combination of the following criteria: reduction in angiomyolipoma volume of ≥ 50% relative to baseline, where angiomyolipoma volume was sum of volumes of all target lesions identified at baseline, and with a confirmatory scan performed approximately 12 weeks later (no sooner than 8 weeks later); no new angiomyolipoma lesions ≥ 1.0 cm in longest diameter were identified; there were no kidney increases in volume > 20% from nadir. The patient did not have any angiomyolipoma-related bleeding of ≥ grade 2. For the everolimus (core/extension periods) treatment group, the baseline means the latest value on or before starting everolimus.	
End point type	Primary
End point timeframe:	
From date of randomization until the earliest date of first documented AML progression, date of further anti-AML medication (including open-label Everolimus)/surgery or up to 5.7 years	

End point values	Everolimus randomized (Core period)	Placebo randomized (Core period)	Everolimus (Core and/or Extension period)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	79	39	112	
Units: Percentage of Participants				
number (confidence interval 95%)	41.8 (30.8 to 53.4)	0 (0 to 9)	58 (48.3 to 67.3)	

Statistical analyses

Statistical analysis title	Superiority Analysis

Statistical analysis description:

Superiority demonstrated between everolimus & placebo for best overall angiomyolipoma response rate

Comparison groups	Placebo randomized (Core period) v Everolimus randomized (Core period)
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Clopper-Pearson
Point estimate	41.8
Confidence interval	
level	95 %
sides	1-sided
upper limit	58.4
Variability estimate	Standard deviation

Notes:

[1] - H0: RREVEROLIMUS ≤ RRPLACEBO versus H1: RREVEROLIMUS > RRPLACEBO where RR is the probability of angiomyolipoma response on everolimus or on placebo.

The test at the one-sided 2.5% level, analyzed in the FAS.

Secondary: Time to Angiomyolipoma Progression as Per Central Radiology Review

End point title	Time to Angiomyolipoma Progression as Per Central Radiology Review

End point description:

Time to angiomyolipoma progression (TTAP) is defined as time from date of randomization to date of first documented angiomyolipoma progression. Angiomyolipoma progression was defined as one or more of the following: Increase from nadir of ≥ 25% in angiomyolipoma volume to value greater than baseline; the appearance of a new angiomyolipoma ≥ 1.0 cm in longest diameter; an increase from nadir of 20% or more in the volume of either kidney to a value greater than baseline; angiomyolipoma-related bleeding grade ≥ 2. For the everolimus (core/extension periods) treatment group, the time to angiomyolipoma progression is defined starting from the start of everolimus. The baseline means the latest value on or before starting everolimus.

End point type	Secondary

End point timeframe:

From date of randomization until the earliest date of first documented AML progression, date of further anti-AML medication (including open-label Everolimus)/surgery or up to about 5.7 years

End point values	Everolimus randomized (Core period)	Placebo randomized (Core period)	Everolimus (Core and/or Extension period)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	79	39	112	
Units: months				
median (confidence interval 95%)	99.99 (99.99 to 999.99)	11.37 (11.07 to 99.99)	99.99 (99.99 to 999.99)	

Statistical analyses

No statistical analyses for this end point

Secondary: Skin Lesion Response rate as Per Investigator (Only Patients With at Least One Skin Lesion at Baseline)

End point title	Skin Lesion Response rate as Per Investigator (Only Patients With at Least One Skin Lesion at Baseline)

End point description:

Skin lesion response rate in the double-blind period was determined only among patients with at least one skin lesion at baseline, and is the percentage of this group of patients with a best overall skin lesion response on the Physician's Global Assessment of Clinical Condition (PGA) of either complete clinical response (CCR) or partial response (PR). A complete clinical response (CCR) requires a grading of 0 indicating the absence of disease (histological confirmation is not required). Grades 1, 2, and 3 constitute partial response, indicating improvement of at least 50 percent, but less than 100 percent improvement. For the everolimus (core/extension periods) treatment group, the baseline means the latest value on or before starting everolimus.

End point type	Secondary

End point timeframe:

From date of randomization until the earliest date of first documented AML progression, date of further anti-AML medication (including open-label Everolimus)/surgery or up to 5.7 years

End point values	Everolimus (Core and/or Extension period)			
Subject group type	Subject analysis set			
Number of subjects analysed	112			
Units: Percentage of participants				
number (confidence interval 95%)	68.2 (58.5 to 76.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with renal impairment

End point title	Percentage of participants with renal impairment

End point description:

Renal Impairment was measured by glomerular filtration rate which was calculated using the Modification of Diet in Renal Disease formula. Percentage of participants with renal impairment was reported. Severe renal impairment was defined as a GFR of <30ml/min/1.73m2.

End point type	Secondary

End point timeframe:

Day 1 up to 28 days after end of treatment

End point values	Everolimus randomized (Core period)	Placebo randomized (Core period)	Everolimus (Core and/or Extension period)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	79	39	112	
Units: Percentage of Participants				
number (not applicable)				
Glomerular filtration rate <30 ml/min/1.73m^2	2.5	7.7	7.1	
Glomerular filtration rate≥ 30 ml/min/1.73m^2	97.5	92.3	92.9	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in plasma angiogenic molecules - Vascular endothelial growth factor (VEGF) marker

End point title	Change From Baseline in plasma angiogenic molecules - Vascular endothelial growth factor (VEGF) marker

End point description:

Blood samples for biomarker assessment were collected immediately prior to study administration. On-treatment samples was compared to baseline samples with the change from baseline.

End point type	Secondary

End point timeframe:

4 weeks, 12 weeks, 24 weeks, 36 weeks 48 weeks, 60 weeks, 72 weeks

End point values	Everolimus randomized (Core period)	Placebo randomized (Core period)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	79	39		
Units: pg/mL				
arithmetic mean (standard deviation)				
Week 4 (n:56, 28)	38.7 (± 141.89)	17.6 (± 57.51)		
Week 12 (n:56, 29)	43.4 (± 60.62)	-6.1 (± 46.28)		
Week 24 (n:53, 29)	31.1 (± 75.83)	-4.3 (± 44.76)		

Week 36 (n:26, 18)	18 (± 45.07)	5.4 (± 24.01)		
Week 48 (n:16, 8)	55.3 (± 80.31)	3.1 (± 34.55)		
Week 60 (n:0, 1)	99.99 (± 999.99)	-4.12 (± 99.99)		
Week 72 (n:0, 1)	99.99 (± 999.99)	-6.1 (± 99.99)		

Statistical analyses

No statistical analyses for this end point

Secondary: Everolimus Trough Concentrations (Cmin)

End point title	Everolimus Trough Concentrations (Cmin)

End point description:

Cmin values collected prior to dose administration on the same study day and at 20-28 hours after previous dose, at steady state, and patient did not vomit within 4 hours of previous dose. Samples collected during the first 4 days of dosing were excluded from all analyses.

End point type	Secondary

End point timeframe:

Prior to dosing at weeks 2, 4, 12, 24, 48

End point values	Everolimus randomized (Core period)			
Subject group type	Subject analysis set			
Number of subjects analysed	79			
Units: ng/mL				
arithmetic mean (standard deviation)				
Prior to dosing at Week 2 (n:43)	7.63 (± 4.32)			
Prior to dosing Week 4 (n:44)	7.72 (± 4.35)			
Prior to dosing Week 12 (n:49)	8.79 (± 6.75)			
Prior to dosing Week 24 (n:46)	9.37 (± 8.83)			
Prior to dosing Week 48 (n:15)	11.49 (± 12.01)			

Statistical analyses

No statistical analyses for this end point

Secondary: Everolimus blood Concentrations (C2h) at 2 hours post-dose

End point title	Everolimus blood Concentrations (C2h) at 2 hours post-dose

End point description:

C2h values collected 1-3 hours after dose administration on the same study day, at steady state, and patient did not vomit between taking previous dose and blood collection. Samples collected during the first 4 days of dosing will be excluded from all analyses.

End point type	Secondary

End point timeframe:

2 hours post-dose administration at Weeks 2, 4, 12, 24, 48

End point values	Everolimus randomized (Core period)			
Subject group type	Subject analysis set			
Number of subjects analysed	79			
Units: ng/mL				
arithmetic mean (standard deviation)				
2 hours post dose administration at Week 2 (n:55)	33.38 (± 15.66)			
2 hours post dose administration at Week 4 (n:49)	30.89 (± 14.96)			
2 hours post dose administration at Week 12 (n:56)	34.48 (± 15.1)			
2 hours post dose administration at Week 24 (n:50)	39.27 (± 22.25)			
2 hours post dose administration at Week 48 (n:14)	33.2 (± 18.45)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to angiomyolipoma response - only Everolimus patients with angiomyolipoma response

End point title	Time to angiomyolipoma response - only Everolimus patients with angiomyolipoma response

End point description:

Time to angiomyolipoma response was defined as the time from the date of randomization until the date of the first documented angiomyolipoma response. Angiomyolipoma response defined as the combination of the following criteria: reduction in angiomyolipoma volume of ≥ 50% relative to baseline, where angiomyolipoma volume was sum of volumes of all target lesions identified at baseline, and with a confirmatory scan performed approximately 12 weeks later (no sooner than 8 weeks later); no new angiomyolipoma lesions ≥ 1.0 cm in longest diameter were identified; no kidney increases in volume > 20% from nadir; no angiomyolipoma-related bleeding of ≥ grade 2. For the everolimus (core/extension periods) treatment group, the time to angiomyolipoma response is from the start of everolimus. The baseline in the response definition means the latest value on or before starting everolimus.

End point type	Secondary

End point timeframe:

From date of randomization until the earliest date of first documented AML progression, date of further anti-AML medication (including open-label Everolimus)/surgery or up to 5.7 years

End point values	Everolimus (Core and/or Extension period)			
Subject group type	Subject analysis set			
Number of subjects analysed	65			
Units: months				
median (confidence interval 95%)	2.89 (2.79 to 3.19)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of angiomyolipoma response - only Everolimus patients with angiomyolipoma response

End point title	Duration of angiomyolipoma response - only Everolimus patients with angiomyolipoma response

End point description:

Duration of angiomyolipoma response was defined as the time from the date of the first documented angiomyolipoma response until the date of the first documented angiomyolipoma progression . Angiomyolipoma response was defined as the combination of the following criteria: reduction in angiomyolipoma volume of ≥ 50% relative to baseline, where angiomyolipoma volume was sum of volumes of all target lesions identified at baseline, and with a confirmatory scan performed approximately 12 weeks later (no sooner than 8 weeks later); no new angiomyolipoma lesions ≥ 1.0 cm in longest diameter were identified; there were no kidney increases in volume > 20% from nadir. The patient did not have any angiomyolipoma-related bleeding of ≥ grade 2.

End point type	Secondary

End point timeframe:

From date of randomization until the earliest date of first documented AML progression, date of further anti-AML medication (including open-label Everolimus)/surgery or up to about 5.7 years

End point values	Everolimus (Core and/or Extension period)			
Subject group type	Subject analysis set			
Number of subjects analysed	65			
Units: months				
median (confidence interval 95%)	99.99 (99.99 to 999.99)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of skin lesion response - only Everolimus patients with best overall skin lesion response of Complete clinical response (CCR) or Partial response (PR)

End point title	Duration of skin lesion response - only Everolimus patients with best overall skin lesion response of Complete clinical response (CCR) or Partial response (PR)

End point description:

Duration of skin lesion response is defined as the time from the date of the first skin lesion response until the date of the first skin lesion progression, according to the PGA (physician’s global assessment of clinical condition). A progression is when the disease is worse than at baseline evaluation by >=25% or more.

End point type	Secondary

End point timeframe:

From date of randomization until the earliest date of first documented AML progression, date of further anti-AML medication (including open-label Everolimus)/surgery or up to about 5.7 years

End point values	Everolimus (Core and/or Extension period)			
Subject group type	Subject analysis set			
Number of subjects analysed	73			
Units: months				
median (confidence interval 95%)	99.99 (99.99 to 999.99)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Timeframe for AE	
Adverse event reporting additional description:	
AE additional description	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups	
Reporting group title	Randomized to everolimus
Reporting group description:	
Randomized to everolimus	
Reporting group title	Randomized to placebo and crossed-over to everolimus
Reporting group description:	
Randomized to placebo and crossed-over to everolimus	
Reporting group title	Randomized to placebo and never crossed-over to everolimus
Reporting group description:	
Randomized to placebo and never crossed-over to everolimus	

Serious adverse events	Randomized to everolimus	Randomized to placebo and crossed-over to everolimus	Randomized to placebo and never crossed-over to everolimus
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 79 (35.44%)	17 / 33 (51.52%)	3 / 6 (50.00%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Angiomyolipoma			
subjects affected / exposed	0 / 79 (0.00%)	0 / 33 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal sinus cancer			
subjects affected / exposed	1 / 79 (1.27%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic carcinoma			

subjects affected / exposed	1 / 79 (1.27%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	1 / 79 (1.27%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemodynamic instability			
subjects affected / exposed	0 / 79 (0.00%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 79 (0.00%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	1 / 79 (1.27%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis			
subjects affected / exposed	1 / 79 (1.27%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	0 / 79 (0.00%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	1 / 79 (1.27%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 79 (1.27%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Breast hypoplasia			
subjects affected / exposed	0 / 79 (0.00%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial hyperplasia			
subjects affected / exposed	0 / 79 (0.00%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cyst			
subjects affected / exposed	1 / 79 (1.27%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cyst ruptured			
subjects affected / exposed	0 / 79 (0.00%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	1 / 79 (1.27%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 79 (0.00%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleuritic pain			

subjects affected / exposed	1 / 79 (1.27%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	2 / 79 (2.53%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Affective disorder			
subjects affected / exposed	0 / 79 (0.00%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aggression			
subjects affected / exposed	0 / 79 (0.00%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alcohol abuse			
subjects affected / exposed	0 / 79 (0.00%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			
subjects affected / exposed	1 / 79 (1.27%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hallucination			
subjects affected / exposed	1 / 79 (1.27%)	0 / 33 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric decompensation			
subjects affected / exposed	0 / 79 (0.00%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychogenic seizure			

subjects affected / exposed	0 / 79 (0.00%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic disorder			
subjects affected / exposed	1 / 79 (1.27%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood creatinine increased			
subjects affected / exposed	2 / 79 (2.53%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 79 (1.27%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	1 / 79 (1.27%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	0 / 79 (0.00%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiovascular insufficiency			
subjects affected / exposed	1 / 79 (1.27%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Complex regional pain syndrome			

subjects affected / exposed	1 / 79 (1.27%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Convulsion			
subjects affected / exposed	1 / 79 (1.27%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Diplegia			
subjects affected / exposed	1 / 79 (1.27%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	3 / 79 (3.80%)	3 / 33 (9.09%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised tonic-clonic seizure			
subjects affected / exposed	2 / 79 (2.53%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrocephalus			
subjects affected / exposed	0 / 79 (0.00%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 79 (1.27%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	1 / 79 (1.27%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Bone marrow oedema			

subjects affected / exposed	1 / 79 (1.27%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	0 / 79 (0.00%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Visual acuity reduced			
subjects affected / exposed	1 / 79 (1.27%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal adhesions			
subjects affected / exposed	0 / 79 (0.00%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal compartment syndrome			
subjects affected / exposed	0 / 79 (0.00%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal hernia			
subjects affected / exposed	1 / 79 (1.27%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	1 / 79 (1.27%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 79 (1.27%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Diarrhoea			
subjects affected / exposed	1 / 79 (1.27%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea haemorrhagic			
subjects affected / exposed	1 / 79 (1.27%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer			
subjects affected / exposed	0 / 79 (0.00%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileal perforation			
subjects affected / exposed	0 / 79 (0.00%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			
subjects affected / exposed	0 / 79 (0.00%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salivary gland calculus			
subjects affected / exposed	1 / 79 (1.27%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Volvulus			
subjects affected / exposed	0 / 79 (0.00%)	0 / 33 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 79 (1.27%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			

Bile duct stenosis			
subjects affected / exposed	1 / 79 (1.27%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 79 (1.27%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	1 / 79 (1.27%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure chronic			
subjects affected / exposed	0 / 79 (0.00%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal haemorrhage			
subjects affected / exposed	0 / 79 (0.00%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	0 / 79 (0.00%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 79 (0.00%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chondropathy			

subjects affected / exposed	1 / 79 (1.27%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint effusion			
subjects affected / exposed	2 / 79 (2.53%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhabdomyolysis			
subjects affected / exposed	0 / 79 (0.00%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal osteoarthritis			
subjects affected / exposed	1 / 79 (1.27%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess			
subjects affected / exposed	1 / 79 (1.27%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	2 / 79 (2.53%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 79 (0.00%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopneumonia			
subjects affected / exposed	1 / 79 (1.27%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Campylobacter gastroenteritis			

subjects affected / exposed	1 / 79 (1.27%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 79 (0.00%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 79 (0.00%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal infection			
subjects affected / exposed	1 / 79 (1.27%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incision site infection			
subjects affected / exposed	0 / 79 (0.00%)	0 / 33 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 79 (0.00%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 79 (1.27%)	3 / 33 (9.09%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	1 / 79 (1.27%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			

subjects affected / exposed	0 / 79 (0.00%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	0 / 79 (0.00%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 79 (1.27%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 79 (0.00%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 79 (1.27%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gout			
subjects affected / exposed	1 / 79 (1.27%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Randomized to everolimus	Randomized to placebo and crossed-over to everolimus	Randomized to placebo and never crossed-over to everolimus
Total subjects affected by non-serious adverse events			
subjects affected / exposed	79 / 79 (100.00%)	33 / 33 (100.00%)	5 / 6 (83.33%)
Vascular disorders			
Circulatory collapse			

subjects affected / exposed	2 / 79 (2.53%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	2	2	0
Haematoma			
subjects affected / exposed	2 / 79 (2.53%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	2	2	0
Hypertension			
subjects affected / exposed	22 / 79 (27.85%)	12 / 33 (36.36%)	0 / 6 (0.00%)
occurrences (all)	24	15	0
Lymphoedema			
subjects affected / exposed	4 / 79 (5.06%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	4	3	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 79 (2.53%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	3	2	0
Fatigue			
subjects affected / exposed	17 / 79 (21.52%)	13 / 33 (39.39%)	1 / 6 (16.67%)
occurrences (all)	22	15	1
Influenza like illness			
subjects affected / exposed	2 / 79 (2.53%)	5 / 33 (15.15%)	1 / 6 (16.67%)
occurrences (all)	2	13	1
Malaise			
subjects affected / exposed	0 / 79 (0.00%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Oedema peripheral			
subjects affected / exposed	16 / 79 (20.25%)	10 / 33 (30.30%)	0 / 6 (0.00%)
occurrences (all)	31	19	0
Pyrexia			
subjects affected / exposed	11 / 79 (13.92%)	6 / 33 (18.18%)	1 / 6 (16.67%)
occurrences (all)	16	7	1
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 79 (1.27%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	1	2	0
Seasonal allergy			

subjects affected / exposed	3 / 79 (3.80%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	3	3	0
Reproductive system and breast disorders			
Amenorrhoea			
subjects affected / exposed	16 / 79 (20.25%)	6 / 33 (18.18%)	0 / 6 (0.00%)
occurrences (all)	30	8	0
Dysmenorrhoea			
subjects affected / exposed	3 / 79 (3.80%)	1 / 33 (3.03%)	1 / 6 (16.67%)
occurrences (all)	3	5	1
Menorrhagia			
subjects affected / exposed	11 / 79 (13.92%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	23	2	0
Menstruation irregular			
subjects affected / exposed	11 / 79 (13.92%)	4 / 33 (12.12%)	0 / 6 (0.00%)
occurrences (all)	11	4	0
Metrorrhagia			
subjects affected / exposed	4 / 79 (5.06%)	3 / 33 (9.09%)	0 / 6 (0.00%)
occurrences (all)	6	4	0
Ovarian cyst			
subjects affected / exposed	5 / 79 (6.33%)	3 / 33 (9.09%)	0 / 6 (0.00%)
occurrences (all)	7	4	0
Vaginal haemorrhage			
subjects affected / exposed	7 / 79 (8.86%)	5 / 33 (15.15%)	0 / 6 (0.00%)
occurrences (all)	13	13	0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	2 / 79 (2.53%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	2	2	0
Cough			
subjects affected / exposed	21 / 79 (26.58%)	7 / 33 (21.21%)	2 / 6 (33.33%)
occurrences (all)	28	9	2
Dyspnoea			
subjects affected / exposed	3 / 79 (3.80%)	3 / 33 (9.09%)	0 / 6 (0.00%)
occurrences (all)	3	3	0
Epistaxis			

subjects affected / exposed	10 / 79 (12.66%)	3 / 33 (9.09%)	0 / 6 (0.00%)
occurrences (all)	12	3	0
Lymphangioleiomyomatosis			
subjects affected / exposed	1 / 79 (1.27%)	1 / 33 (3.03%)	1 / 6 (16.67%)
occurrences (all)	1	1	1
Nasal congestion			
subjects affected / exposed	2 / 79 (2.53%)	1 / 33 (3.03%)	1 / 6 (16.67%)
occurrences (all)	3	1	1
Oropharyngeal pain			
subjects affected / exposed	13 / 79 (16.46%)	6 / 33 (18.18%)	1 / 6 (16.67%)
occurrences (all)	19	13	1
Pneumothorax			
subjects affected / exposed	0 / 79 (0.00%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Productive cough			
subjects affected / exposed	1 / 79 (1.27%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	2	3	0
Rhinitis allergic			
subjects affected / exposed	2 / 79 (2.53%)	3 / 33 (9.09%)	0 / 6 (0.00%)
occurrences (all)	2	3	0
Rhinorrhoea			
subjects affected / exposed	4 / 79 (5.06%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences (all)	5	0	0
Sinus congestion			
subjects affected / exposed	2 / 79 (2.53%)	1 / 33 (3.03%)	1 / 6 (16.67%)
occurrences (all)	2	1	1
Psychiatric disorders			
Affective disorder			
subjects affected / exposed	0 / 79 (0.00%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Aggression			
subjects affected / exposed	1 / 79 (1.27%)	3 / 33 (9.09%)	0 / 6 (0.00%)
occurrences (all)	1	3	0
Anxiety			
subjects affected / exposed	4 / 79 (5.06%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences (all)	5	1	0

Depression			
subjects affected / exposed	8 / 79 (10.13%)	4 / 33 (12.12%)	0 / 6 (0.00%)
occurrences (all)	9	4	0
Insomnia			
subjects affected / exposed	6 / 79 (7.59%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences (all)	7	1	0
Mood swings			
subjects affected / exposed	3 / 79 (3.80%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	4	2	0
Sleep disorder			
subjects affected / exposed	2 / 79 (2.53%)	3 / 33 (9.09%)	0 / 6 (0.00%)
occurrences (all)	3	5	0
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	10 / 79 (12.66%)	5 / 33 (15.15%)	0 / 6 (0.00%)
occurrences (all)	14	8	0
Alanine aminotransferase increased			
subjects affected / exposed	9 / 79 (11.39%)	5 / 33 (15.15%)	0 / 6 (0.00%)
occurrences (all)	14	10	0
Aspartate aminotransferase increased			
subjects affected / exposed	10 / 79 (12.66%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	11	7	0
Blood alkaline phosphatase increased			
subjects affected / exposed	11 / 79 (13.92%)	5 / 33 (15.15%)	0 / 6 (0.00%)
occurrences (all)	22	5	0
Blood cholesterol increased			
subjects affected / exposed	11 / 79 (13.92%)	3 / 33 (9.09%)	0 / 6 (0.00%)
occurrences (all)	12	9	0
Blood creatine phosphokinase increased			
subjects affected / exposed	3 / 79 (3.80%)	5 / 33 (15.15%)	0 / 6 (0.00%)
occurrences (all)	4	9	0
Blood creatinine increased			
subjects affected / exposed	4 / 79 (5.06%)	4 / 33 (12.12%)	0 / 6 (0.00%)
occurrences (all)	7	5	0
Blood fibrinogen increased			

subjects affected / exposed	4 / 79 (5.06%)	5 / 33 (15.15%)	0 / 6 (0.00%)
occurrences (all)	4	5	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	9 / 79 (11.39%)	4 / 33 (12.12%)	0 / 6 (0.00%)
occurrences (all)	15	4	0
Blood phosphorus decreased			
subjects affected / exposed	6 / 79 (7.59%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences (all)	7	2	0
Blood triglycerides increased			
subjects affected / exposed	10 / 79 (12.66%)	4 / 33 (12.12%)	0 / 6 (0.00%)
occurrences (all)	10	7	0
C-reactive protein increased			
subjects affected / exposed	3 / 79 (3.80%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	3	2	0
Carbon monoxide diffusing capacity decreased			
subjects affected / exposed	7 / 79 (8.86%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences (all)	8	1	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	5 / 79 (6.33%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences (all)	5	1	0
Haemoglobin decreased			
subjects affected / exposed	11 / 79 (13.92%)	3 / 33 (9.09%)	0 / 6 (0.00%)
occurrences (all)	14	5	0
International normalised ratio increased			
subjects affected / exposed	4 / 79 (5.06%)	3 / 33 (9.09%)	0 / 6 (0.00%)
occurrences (all)	4	3	0
Low density lipoprotein increased			
subjects affected / exposed	1 / 79 (1.27%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	1	2	0
Weight decreased			
subjects affected / exposed	7 / 79 (8.86%)	4 / 33 (12.12%)	0 / 6 (0.00%)
occurrences (all)	7	4	0
Weight increased			

subjects affected / exposed	4 / 79 (5.06%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences (all)	4	0	0
White blood cell count decreased			
subjects affected / exposed	1 / 79 (1.27%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	3	3	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 79 (0.00%)	3 / 33 (9.09%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Fall			
subjects affected / exposed	2 / 79 (2.53%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	2	2	0
Incision site pain			
subjects affected / exposed	0 / 79 (0.00%)	0 / 33 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Laceration			
subjects affected / exposed	3 / 79 (3.80%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	4	2	0
Procedural pain			
subjects affected / exposed	2 / 79 (2.53%)	2 / 33 (6.06%)	1 / 6 (16.67%)
occurrences (all)	2	2	1
Congenital, familial and genetic disorders			
Hamartoma			
subjects affected / exposed	1 / 79 (1.27%)	3 / 33 (9.09%)	0 / 6 (0.00%)
occurrences (all)	1	3	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 79 (0.00%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Tachycardia			
subjects affected / exposed	2 / 79 (2.53%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	3	2	0
Nervous system disorders			
Convulsion			
subjects affected / exposed	8 / 79 (10.13%)	4 / 33 (12.12%)	0 / 6 (0.00%)
occurrences (all)	11	15	0

Dizziness			
subjects affected / exposed	9 / 79 (11.39%)	4 / 33 (12.12%)	1 / 6 (16.67%)
occurrences (all)	10	5	1
Epilepsy			
subjects affected / exposed	3 / 79 (3.80%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	3	3	0
Headache			
subjects affected / exposed	26 / 79 (32.91%)	15 / 33 (45.45%)	0 / 6 (0.00%)
occurrences (all)	54	34	0
Lethargy			
subjects affected / exposed	1 / 79 (1.27%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	1	2	0
Migraine			
subjects affected / exposed	9 / 79 (11.39%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences (all)	19	1	0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 79 (0.00%)	3 / 33 (9.09%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Petit mal epilepsy			
subjects affected / exposed	4 / 79 (5.06%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	4	10	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	9 / 79 (11.39%)	6 / 33 (18.18%)	0 / 6 (0.00%)
occurrences (all)	16	7	0
Leukopenia			
subjects affected / exposed	9 / 79 (11.39%)	7 / 33 (21.21%)	0 / 6 (0.00%)
occurrences (all)	20	17	0
Lymphopenia			
subjects affected / exposed	5 / 79 (6.33%)	5 / 33 (15.15%)	0 / 6 (0.00%)
occurrences (all)	14	11	0
Neutropenia			
subjects affected / exposed	7 / 79 (8.86%)	4 / 33 (12.12%)	0 / 6 (0.00%)
occurrences (all)	15	11	0
Thrombocytopenia			

subjects affected / exposed	6 / 79 (7.59%)	3 / 33 (9.09%)	0 / 6 (0.00%)
occurrences (all)	11	4	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	3 / 79 (3.80%)	4 / 33 (12.12%)	0 / 6 (0.00%)
occurrences (all)	6	7	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	13 / 79 (16.46%)	5 / 33 (15.15%)	2 / 6 (33.33%)
occurrences (all)	17	12	2
Abdominal pain upper			
subjects affected / exposed	7 / 79 (8.86%)	4 / 33 (12.12%)	1 / 6 (16.67%)
occurrences (all)	7	9	1
Aphthous stomatitis			
subjects affected / exposed	19 / 79 (24.05%)	12 / 33 (36.36%)	1 / 6 (16.67%)
occurrences (all)	57	27	1
Constipation			
subjects affected / exposed	8 / 79 (10.13%)	6 / 33 (18.18%)	1 / 6 (16.67%)
occurrences (all)	10	6	1
Dental caries			
subjects affected / exposed	1 / 79 (1.27%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	1	2	0
Diarrhoea			
subjects affected / exposed	17 / 79 (21.52%)	11 / 33 (33.33%)	1 / 6 (16.67%)
occurrences (all)	27	20	1
Dyspepsia			
subjects affected / exposed	4 / 79 (5.06%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences (all)	4	0	0
Flatulence			
subjects affected / exposed	5 / 79 (6.33%)	3 / 33 (9.09%)	0 / 6 (0.00%)
occurrences (all)	5	3	0
Gastrooesophageal reflux disease			
subjects affected / exposed	4 / 79 (5.06%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences (all)	4	0	0
Mouth ulceration			

subjects affected / exposed	15 / 79 (18.99%)	4 / 33 (12.12%)	1 / 6 (16.67%)
occurrences (all)	33	13	1
Nausea			
subjects affected / exposed	18 / 79 (22.78%)	7 / 33 (21.21%)	2 / 6 (33.33%)
occurrences (all)	35	14	2
Stomatitis			
subjects affected / exposed	41 / 79 (51.90%)	10 / 33 (30.30%)	0 / 6 (0.00%)
occurrences (all)	105	14	0
Toothache			
subjects affected / exposed	5 / 79 (6.33%)	3 / 33 (9.09%)	0 / 6 (0.00%)
occurrences (all)	7	6	0
Vomiting			
subjects affected / exposed	18 / 79 (22.78%)	5 / 33 (15.15%)	0 / 6 (0.00%)
occurrences (all)	37	9	0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	25 / 79 (31.65%)	11 / 33 (33.33%)	0 / 6 (0.00%)
occurrences (all)	34	15	0
Alopecia			
subjects affected / exposed	7 / 79 (8.86%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	7	2	0
Dermatitis			
subjects affected / exposed	4 / 79 (5.06%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences (all)	4	9	0
Dermatitis acneiform			
subjects affected / exposed	6 / 79 (7.59%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences (all)	13	1	0
Dry skin			
subjects affected / exposed	8 / 79 (10.13%)	5 / 33 (15.15%)	0 / 6 (0.00%)
occurrences (all)	8	5	0
Eczema			
subjects affected / exposed	11 / 79 (13.92%)	3 / 33 (9.09%)	0 / 6 (0.00%)
occurrences (all)	14	4	0
Papule			
subjects affected / exposed	4 / 79 (5.06%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	4	2	0

Pigmentation disorder			
subjects affected / exposed	4 / 79 (5.06%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	4	2	0
Pruritus			
subjects affected / exposed	8 / 79 (10.13%)	5 / 33 (15.15%)	0 / 6 (0.00%)
occurrences (all)	10	5	0
Rash			
subjects affected / exposed	5 / 79 (6.33%)	3 / 33 (9.09%)	0 / 6 (0.00%)
occurrences (all)	7	3	0
Rash pruritic			
subjects affected / exposed	1 / 79 (1.27%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	1	5	0
Skin mass			
subjects affected / exposed	0 / 79 (0.00%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	2 / 79 (2.53%)	3 / 33 (9.09%)	1 / 6 (16.67%)
occurrences (all)	7	4	1
Leukocyturia			
subjects affected / exposed	0 / 79 (0.00%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Proteinuria			
subjects affected / exposed	11 / 79 (13.92%)	10 / 33 (30.30%)	0 / 6 (0.00%)
occurrences (all)	16	28	0
Renal pain			
subjects affected / exposed	0 / 79 (0.00%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	13 / 79 (16.46%)	3 / 33 (9.09%)	0 / 6 (0.00%)
occurrences (all)	19	3	0
Back pain			
subjects affected / exposed	12 / 79 (15.19%)	14 / 33 (42.42%)	0 / 6 (0.00%)
occurrences (all)	18	16	0
Flank pain			

subjects affected / exposed	5 / 79 (6.33%)	5 / 33 (15.15%)	1 / 6 (16.67%)
occurrences (all)	7	8	1
Muscle spasms			
subjects affected / exposed	2 / 79 (2.53%)	2 / 33 (6.06%)	1 / 6 (16.67%)
occurrences (all)	2	3	1
Musculoskeletal chest pain			
subjects affected / exposed	1 / 79 (1.27%)	4 / 33 (12.12%)	0 / 6 (0.00%)
occurrences (all)	1	4	0
Musculoskeletal pain			
subjects affected / exposed	2 / 79 (2.53%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	4	5	0
Myalgia			
subjects affected / exposed	7 / 79 (8.86%)	5 / 33 (15.15%)	1 / 6 (16.67%)
occurrences (all)	12	5	1
Neck pain			
subjects affected / exposed	1 / 79 (1.27%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	1	3	0
Pain in extremity			
subjects affected / exposed	5 / 79 (6.33%)	7 / 33 (21.21%)	0 / 6 (0.00%)
occurrences (all)	5	10	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	9 / 79 (11.39%)	9 / 33 (27.27%)	1 / 6 (16.67%)
occurrences (all)	11	13	1
Cellulitis			
subjects affected / exposed	2 / 79 (2.53%)	4 / 33 (12.12%)	0 / 6 (0.00%)
occurrences (all)	3	4	0
Conjunctivitis			
subjects affected / exposed	4 / 79 (5.06%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	5	2	0
Ear infection			
subjects affected / exposed	5 / 79 (6.33%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences (all)	5	1	0
Folliculitis			
subjects affected / exposed	4 / 79 (5.06%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences (all)	4	1	0

Furuncle			
subjects affected / exposed	4 / 79 (5.06%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	4	2	0
Gastroenteritis			
subjects affected / exposed	9 / 79 (11.39%)	4 / 33 (12.12%)	0 / 6 (0.00%)
occurrences (all)	9	4	0
Gastroenteritis viral			
subjects affected / exposed	4 / 79 (5.06%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences (all)	6	0	0
Gastrointestinal infection			
subjects affected / exposed	1 / 79 (1.27%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	1	2	0
Gingivitis			
subjects affected / exposed	2 / 79 (2.53%)	3 / 33 (9.09%)	0 / 6 (0.00%)
occurrences (all)	3	3	0
Influenza			
subjects affected / exposed	8 / 79 (10.13%)	3 / 33 (9.09%)	1 / 6 (16.67%)
occurrences (all)	8	4	1
Nasopharyngitis			
subjects affected / exposed	36 / 79 (45.57%)	19 / 33 (57.58%)	1 / 6 (16.67%)
occurrences (all)	102	58	2
Oral candidiasis			
subjects affected / exposed	1 / 79 (1.27%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	3	2	0
Oral herpes			
subjects affected / exposed	5 / 79 (6.33%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences (all)	14	2	0
Otitis externa			
subjects affected / exposed	0 / 79 (0.00%)	3 / 33 (9.09%)	0 / 6 (0.00%)
occurrences (all)	0	4	0
Otitis media			
subjects affected / exposed	6 / 79 (7.59%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	13	4	0
Periodontitis			
subjects affected / exposed	6 / 79 (7.59%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences (all)	7	0	0

Pharyngitis			
subjects affected / exposed	5 / 79 (6.33%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences (all)	6	1	0
Pharyngitis streptococcal			
subjects affected / exposed	5 / 79 (6.33%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences (all)	8	0	0
Pneumonia			
subjects affected / exposed	6 / 79 (7.59%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	7	2	0
Rash pustular			
subjects affected / exposed	7 / 79 (8.86%)	3 / 33 (9.09%)	0 / 6 (0.00%)
occurrences (all)	8	3	0
Respiratory tract infection			
subjects affected / exposed	5 / 79 (6.33%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	5	2	0
Respiratory tract infection viral			
subjects affected / exposed	5 / 79 (6.33%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences (all)	8	0	0
Rhinitis			
subjects affected / exposed	7 / 79 (8.86%)	6 / 33 (18.18%)	1 / 6 (16.67%)
occurrences (all)	12	7	1
Sinusitis			
subjects affected / exposed	11 / 79 (13.92%)	4 / 33 (12.12%)	1 / 6 (16.67%)
occurrences (all)	27	10	1
Tonsillitis			
subjects affected / exposed	1 / 79 (1.27%)	6 / 33 (18.18%)	0 / 6 (0.00%)
occurrences (all)	1	6	0
Tooth abscess			
subjects affected / exposed	7 / 79 (8.86%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	10	2	0
Tooth infection			
subjects affected / exposed	4 / 79 (5.06%)	3 / 33 (9.09%)	0 / 6 (0.00%)
occurrences (all)	5	3	0
Upper respiratory tract infection			
subjects affected / exposed	15 / 79 (18.99%)	4 / 33 (12.12%)	0 / 6 (0.00%)
occurrences (all)	24	10	0

Urinary tract infection			
subjects affected / exposed	25 / 79 (31.65%)	12 / 33 (36.36%)	1 / 6 (16.67%)
occurrences (all)	50	23	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	8 / 79 (10.13%)	6 / 33 (18.18%)	0 / 6 (0.00%)
occurrences (all)	8	6	0
Hypercholesterolaemia			
subjects affected / exposed	29 / 79 (36.71%)	11 / 33 (33.33%)	0 / 6 (0.00%)
occurrences (all)	40	23	0
Hyperglycaemia			
subjects affected / exposed	3 / 79 (3.80%)	4 / 33 (12.12%)	0 / 6 (0.00%)
occurrences (all)	3	7	0
Hyperlipidaemia			
subjects affected / exposed	10 / 79 (12.66%)	5 / 33 (15.15%)	0 / 6 (0.00%)
occurrences (all)	19	6	0
Hypertriglyceridaemia			
subjects affected / exposed	8 / 79 (10.13%)	4 / 33 (12.12%)	0 / 6 (0.00%)
occurrences (all)	8	7	0
Hypokalaemia			
subjects affected / exposed	2 / 79 (2.53%)	5 / 33 (15.15%)	0 / 6 (0.00%)
occurrences (all)	2	5	0
Hypophosphataemia			
subjects affected / exposed	15 / 79 (18.99%)	4 / 33 (12.12%)	0 / 6 (0.00%)
occurrences (all)	26	4	0
Iron deficiency			
subjects affected / exposed	7 / 79 (8.86%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences (all)	7	2	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 March 2010	Amendment 1 was issued after the inclusion of 21% of patients and introduced the following changes: Allowed assessment of angiomyolipomas to be carried out by CT scan as well as by MRI with the condition that the same imaging modality for assessment of the kidneys must be used throughout the trial for each individual patient; Patients who met pre-specified criteria at BL would now be screened for hepatitis B (HBV) and hepatitis C (HCV) at BL, using the following tests: HBV DNA, HBV surface antigen, HBV surface antibody, HBV core antibody, HCV RNA-PCR. Hepatitis B and C management guidelines were added for patients who are active prior to the implementation of Amendment 1; Harmonized the visit window for all visits; Added revised table of p-glycoprotein substrates, inhibitors, and inducers; Added provision for an End of Treatment scan if the patient discontinued for reasons other than progression and enough time had passed since their most recent scan; Added instructions for the permitted local laboratory collections for the 6 week visit for patients in the United States for whom travel to the clinic was difficult; Changed the requirement of a confirmatory scan from "at least 4 weeks" after the first assessment of response to "approximately 12" (and no sooner than 8 weeks) after the first assessment of response; Changed the confirmation of skin lesion response from "at least 4 weeks" after the first response assessment to "approximately 12 weeks" (and no sooner than 8 weeks) after the first response assessment; Added the following exclusion criteria: Patients with angiomyolipoma which, in the opinion of the Investigator, requires surgery at the time of randomization; Any severe and/or uncontrolled medical conditions which could cause unacceptable safety risks or compromise compliance with the protocol; Modified the exclusion criterion on impaired lung function to define separate thresholds for patients with and without LAM;
29 March 2010	Amendment 1 (continued): Replaced PFTs at BL and at every trial visit with PFTs at BL for all LAM patients, and PFTs to be performed 1) as clinically indicated in patients without LAM and 2) at 6, 12, 18 and 24 weeks and every 12 weeks thereafter, for patients with LAM. Removed the requirement for chest CT at BL for patients who are unable to perform PFTs; Modified the definition of angiomyolipoma progression to not only an increase from nadir of 25% or more in angiomyolipoma volume, but also to a value greater than BL angiomyolipoma volume; of 20% or more in the volume of either kidney to a value greater than BL, where nadir was the lowest kidney volume obtained for the patient, separately for each kidney, previously in the trial (including BL); Modified the definition of SEGA progression to be not only an increase from nadir of 25% or more in SEGA volume, but also to a value greater than BL SEGA volume; Increased from 3 to 6 weeks the amount of time off study drug (e.g. for an AE or surgery) which was permitted before a patient was discontinued from the trial; Increased the screening period from 14 to 21 days; permitted screening blood tests carried out within 14 days of Treatment Day 1 to be used for BL values; Required a urine pregnancy screen at Treatment Day 1 and added follow-up urine pregnancy tests to be conducted every 12 weeks after the start of study drug; Added LH, FSH, and testosterone levels in all patients and estradiol levels in all female patients at Screening and every 24 weeks after the start of study drug.

22 August 2012	Amendment 3 contained administrative changes to the Visit Evaluation Schedules as well as editorial changes and clarifications: Changed inclusion criteria to include highly effective contraceptive measures instead of adequate contraceptive measures; Added secondary amenorrhea as an identified risk of study drug. Added information on management of secondary amenorrhea; Added detailed description of highly effective contraceptive measures; Revised visit schedule and assessment for urine pregnancy, serum pregnancy, and endocrine testing; Revised Additional menstrual history and pregnancy history information collected. Will conduct monthly monitoring of menstrual status; Added completion of hormone evaluations when amenorrhea is seen between scheduled visits; Reproductive history and endocrine testing section added. Additional medical information on reproductive history will be collected. Endocrine testing information added; Additional safety language for pregnancies added; Information on documentation of at home pregnancy testing and documentation of menstrual status monitoring added.
15 January 2013	Amendment 4 was issued when the enrollment was complete and approximately 100 active patients were being followed in the extension phase of the study. The following paragraph was deleted from the protocol: This amendment is required for patient safety (i.e. necessary to eliminate immediate hazards to the trial subjects ICH Good Clinical Practice 3.3.8). Therefore it will be implemented prior to IRB/IEC approval, but will be sent for approval as well. The following paragraph was added: The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.
24 October 2013	Amendment 5 was issued when the enrollment had been completed and approximately 98 patients had been treated with everolimus in the extension phase of the study. The protocol was amended to add a non-interventional follow-up phase, fulfilling a commitment made to European Medicines Agency, in order to better characterize tumor behavior after discontinuation of everolimus; Administrative change to corrected typo in rationale section for Amendment 4 which previously cited the wrong amendment number; Updated Exploratory objectives to include assessment of tumor characteristics after stopping everolimus treatment; Clarified collection window for concomitant medications/non-drug therapies taken after discontinuing study treatment; Added non-interventional follow-up phase to the study design; Added end of protocol section; Added new study design schema for non-interventional follow-up phase; Added non-interventional follow-up phase inclusion criteria; Added non-interventional follow-up phase exclusion criteria; Clarified that placebo was only used during the blinded phase; Table updated with newest list of cytochrome P450 (CYP)3A4 inhibitors/inducer; Table updated with newest list of PGP inhibitors/inducers; Added new section that describes non-interventional follow-up phase; added new table, revised old tables, updated text to include references to the new table; Added text to clarify when to perform final study treatment-related serum pregnancy testing; New text added to clarify radiological evaluation of non-interventional follow-up phase; New text to clarify the safety data collection in the non-interventional follow-up phase; New text added to clarify the adverse event reporting in non-interventional follow-up phase; Added text to clarify when to perform final study treatment-related serum pregnancy testing; Administrative change to correct data collection as this is a pCRF study and to add methodology for radiological imaging;
24 October 2013	Amendment 5 (continued): Added evaluation after everolimus discontinuation; Administrative changes were made, as needed.

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.

Due to EudraCT system limitations, which EMA is aware of, results of crossover studies and data using 999 as data points are not accurately represented in this record. Please go to https://www.novctrd.com/CtrdWeb/home.nov for complete trial results

Notes: