Clinical trial results:
A randomized, double-blind, placebo-controlled study of RAD001 in the treatment of patients with subependymal giant cell astrocytomas (SEGA) associated with Tuberous Sclerosis Complex (TSC)

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.novfor complete trial results.

Summary

EudraCT number	2007-006997-27
Trial protocol	BE IT GB DE NL
Global end of trial date	02 October 2014

Results information

Result version number	v1 (current)
This version publication date	07 July 2018
First version publication date	07 July 2018

Trial information

Trial identification

Sponsor protocol code	CRAD001M2301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00789828
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)	Yes
EMA paediatric investigation plan number(s)	EMEA-000019-PIP02-07
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 October 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 October 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to evaluate the efficacy and safety of everolimus in treating patients with subependymal giant cell astrocytomas (SEGA) associated with tuberous sclerosis complex (TSC).

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	10 August 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	Australia: 2
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Poland: 19
Country: Number of subjects enrolled	Russian Federation: 12
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	United States: 67
Worldwide total number of subjects	117
EEA total number of subjects	33

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)	13
Children (2-11 years)	61
Adolescents (12-17 years)	27
Adults (18-64 years)	16
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 24 centres in 10 countries.

Pre-assignment

Screening details:

A total of 117 subjects were enrolled and randomized into the core period. Only 111 subjects completing the core period, continued in the open-label extension period of the study.

Period 1

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

Blinding implementation details:

Randomization data were kept strictly confidential and the identity of treatments were concealed by the use of identical study drugs. Unblinding was allowed from randomization to database lock, except in case of patient emergencies and at the conclusion of the study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Everolimus (Core period)

Arm description:

Subjects received oral dose of everolimus 4.5 milligram/square meter (mg/m^2) daily as an initial starting dose to attain the whole blood trough concentrations in range of 5-15 nanogram/millilitre (ng/mL). Dose adjustments were permitted based on safety and whole blood trough concentrations.

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 was administered orally at a starting dose of 4.5 mg/m^2 daily and up-titrated to attain blood trough concentration of 5-15 ng/mL.

Arm title	Placebo (Core period)

Arm description:

Subjects received oral dose of placebo matching to everolimus daily.

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

Dosage and administration details:

Placebo matched to everolimus was administered daily via oral route.

Number of subjects in period 1	Everolimus (Core period)	Placebo (Core period)
Started	78	39
Completed	78	33
Not completed	0	6
Consent withdrawn by subject	-	4
Administrative problems	-	1
Lost to follow-up	-	1

Period 2

Period 2 title	Extension period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

The extension period was open label, hence no blinding was performed.

Arms

Arm title	Everolimus (Extension period)

Arm description:

Subjects received oral dose of everolimus 4.5 mg/m^2 daily as an initial starting dose to attain blood trough concentrations in range of 5-15 ng/mL.

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 was administered at a starting dose of 4.5 mg/m^2 daily and up-titrated to attain blood trough concentration of 5-15 ng/mL.

Number of subjects in period 2	Everolimus (Extension period)
Started	111
Completed	82
Not completed	29
Consent withdrawn by subject	6
Disease progression	1
New treatment for indication under study	1
Adverse event, non-fatal	10
Death	1

Administrative problems	7
Lost to follow-up	3

Baseline characteristics

Reporting groups	
Reporting group title	Everolimus (Core period)
Reporting group description:	
Subjects received oral dose of everolimus 4.5 milligram/square meter (mg/m^2) daily as an initial starting dose to attain the whole blood trough concentrations in range of 5-15 nanogram/millilitre (ng/mL). Dose adjustments were permitted based on safety and whole blood trough concentrations.	
Reporting group title	Placebo (Core period)
Reporting group description:	
Subjects received oral dose of placebo matching to everolimus daily.	

Reporting group values	Everolimus (Core period)	Placebo (Core period)	Total
Number of subjects	78	39	117
Age categorical Units: Subjects			
Age <3 years	13	7	20
Age 3 to <18 years	55	26	81
Age ≥ 18 years	10	6	16
Age continuous Units: years			
arithmetic mean	10.1	10.3	
standard deviation	± 5.9	± 7.3	-
Gender categorical Units: Subjects			
Female	29	21	50
Male	49	18	67

End points

End points reporting groups

Reporting group title	Everolimus (Core period)
Reporting group description:	
Subjects received oral dose of everolimus 4.5 milligram/square meter (mg/m^2) daily as an initial starting dose to attain the whole blood trough concentrations in range of 5-15 nanogram/millilitre (ng/mL). Dose adjustments were permitted based on safety and whole blood trough concentrations.	
Reporting group title	Placebo (Core period)
Reporting group description:	
Subjects received oral dose of placebo matching to everolimus daily.	
Reporting group title	Everolimus (Extension period)
Reporting group description:	
Subjects received oral dose of everolimus 4.5 mg/m^2 daily as an initial starting dose to attain blood trough concentrations in range of 5-15 ng/mL.	

Primary: Percentage of subjects with best overall Subependymal Giant Cell Astrocytomas (SEGA) response

End point title	Percentage of subjects with best overall Subependymal Giant Cell Astrocytomas (SEGA) response
End point description:	
Subjects were assessed for SEGA response, defined as 50% reduction from baseline in SEGA volume (where SEGA volume was the sum of the volumes of all target SEGA lesions identified at baseline, and confirmed with a second scan performed approximately 12 weeks later), no unequivocal worsening of non-target SEGA lesions, no new SEGA lesions (≥ 1 cm in longest diameter), and no new or worsening hydrocephalus. Multi-phase brain MRI was utilised to identify SEGA lesions. SEGA response rate was defined as the percentage of subjects whose best overall status was SEGA response as determined by Independent Central Radiology Review. The Kaplan-Meier estimate was used for determining time to SEGA response. The primary analysis was performed in Full Analysis Set (FAS) population, defined as all randomised subjects involved in the study.	
End point type	Primary
End point timeframe:	
Baseline, Week 12, Week 24, Week 48 (Core period), and annually thereafter up to End of study in the extension period.	

End point values	Everolimus (Core period)	Placebo (Core period)	Everolimus (Extension period)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	78	39	111	
Units: Percentage of subjects				
number (confidence interval 95%)	34.6 (24.2 to 46.2)	0 (0 to 0.9)	57.7 (47.9 to 67)	

Statistical analyses

Statistical analysis title	Response rate difference during core study period

Statistical analysis description:

Null hypothesis suggested response rate of everolimus to be less than or equal to response rate of placebo. Alternative hypothesis suggested the response rate of everolimus to be greater than placebo. P-value was obtained from the one-sided exact Cochran-Mantel-Haenszel test.

Comparison groups	Everolimus (Core period) v Placebo (Core period)
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in response rates
Point estimate	34.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	15.1
upper limit	52.4

Secondary: Change from baseline in frequency of total seizure events per 24 hours at Week 24 in both core and extension period

End point title	Change from baseline in frequency of total seizure events per 24 hours at Week 24 in both core and extension period

End point description:

Seizure frequency per 24 hours was defined as the number of seizures in the electroencephalography (EEG) divided by the number of hours in the EEG, multiplied by 24. Seizure frequency was evaluated using a 24-hour video-EEG. Seizure frequency was listed as missing if the actual EEG recording duration was < 18 hours. The analysis was performed in the FAS population. Missing values were imputed using last observation carried forward approach.

End point type	Secondary

End point timeframe:

Baseline (Core period), Week 24 (Core period), Baseline (Extension period), Week 24 (Extension period)

End point values	Everolimus (Core period)	Placebo (Core period)	Everolimus (Extension period)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	78	39	34	
Units: Seizure frequency				
arithmetic mean (standard deviation)	-1.24 (± 6.12)	-0.24 (± 5.7)	-6.07 (± 9.719)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to SEGA progression

End point title	Time to SEGA progression

End point description:

Time to SEGA progression was defined as time between randomisation to time to first SEGA progression. SEGA progression was defined as either one or more of the following criteria: 1. increase from nadir of ≥ 25% in SEGA volume to a value greater than baseline SEGA volume (where SEGA volume is the sum of the volumes of all target SEGA lesions identified at baseline, and nadir is the lowest SEGA volume obtained for the subject previously in the trial), 2. unequivocal worsening of non-target SEGA lesions, 3. appearance of new SEGA lesion ≥ 1.0 cm in longest diameter, 4. new or worsening hydrocephalus. The analysis was performed in the FAS population. Here "Number of subjects analysed" signifies the subjects assessed for time to SEGA progression during the study for each arm, respectively. The median TTSP based on central radiology review was not reached in any treatment arms; Here, 99999.9 represents not applicable data because EudraCT system is not accepting "NA" for not available data.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 24, Week 48 after start of study treatment, and annually thereafter up to End of study

End point values	Everolimus (Core period)	Placebo (Core period)	Everolimus (Extension period)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	78[1]	39[2]	111[3]	
Units: Months				
median (confidence interval 95%)	99999.9 (-99999.9 to 99999.9)	99999.9 (-99999.9 to 99999.9)	99999.9 (-99999.9 to 99999.9)	

Notes:

[1] - Median was not reached as no subject experienced disease progression during core period.

[2] - Median was not reached as only 6 subjects experienced disease progression during core period.

[3] - Median was not reached as no subject experienced disease progression during extension period.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to SEGA response

End point title	Time to SEGA response[4]

End point description:

Subjects were assessed for time to SEGA response, defined as 50% reduction from baseline in SEGA volume (where SEGA volume was the sum of the volumes of all target SEGA lesions identified at baseline, and confirmed with a second scan performed approximately 12 weeks later), no unequivocal worsening of non-target SEGA lesions, no new SEGA lesions (≥ 1 cm in longest diameter), and no new or worsening hydrocephalus. Multi-phase brain MRI was utilised to identify SEGA lesions. SEGA response rate was defined as the percentage of subjects whose best overall status was SEGA response as determined by Independent Central Radiology Review. The Kaplan-Meier estimate was used for determining time to SEGA response. The analysis was performed in the FAS population.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 24, Week 48 after start of study treatment, and annually thereafter up to End of study

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The end point was planned to evaluate the active treatment (everolimus) arms only.

End point values	Everolimus (Core period)	Everolimus (Extension period)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	64		
Units: Months				
median (confidence interval 95%)	2.99 (2.79 to 5.36)	5.32 (3.02 to 5.59)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of SEGA response

End point title	Duration of SEGA response[5]

End point description:

Duration of SEGA response was defined as time from the date of the first documented SEGA response until date of first documented SEGA progression. Duration of SEGA response was evaluated only for subjects who achieved a SEGA response. The time to SEGA progression was censored if SEGA progression was not observed before the first to occur out of (i) analysis cut-off date (ii) the date when systemic anti-SEGA medication is started, (iii) the date of a SEGA-related surgery or (iv) the date of death. Since, no case of SEGA progression was observed in core study which resulted in censored duration of SEGA response. Only 5 SEGA responders experienced a SEGA progression in extension period. The analysis was performed in the FAS population. Here, "Number of subjects analysed" signifies the subjects assessed for SEGA progression during the study for each arm, respectively. Here, 99999.9 represents not applicable data becasue EudraCT system is not accepting "NA" for not available data.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 24, Week 48 after start of study treatment, and annually thereafter up to End of study

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The end point was planned to evaluate the active treatment (everolimus) arms only.

End point values	Everolimus (Core period)	Everolimus (Extension period)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[6]	5[7]		
Units: Months				
median (confidence interval 95%)	99999.9 (-99999.9 to 99999.9)	99999.9 (-99999.9 to 99999.9)		

Notes:

[6] - Median was not achieved as no case of SEGA progression was observed.

[7] - Median was not achieved as only 5 events of SEGA progression were observed.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to SEGA worsening

End point title	Time to SEGA worsening

End point description:

Time to SEGA worsening was defined as the time from the start of everolimus to date of the first SEGA worsening. SEGA worsening was defined as either; increase from nadir of ≥ 25% in SEGA volume or unequivocal worsening of non-target SEGA lesions, or appearance of new SEGA lesion ≥ 1.0 cm in longest diameter, or new or worsening hydrocephalus. The median value was not reached in either treatment arm of core period as SEGA worsening was observed in less subjects (everolimus - 7 and placebo - 8). The analysis was performed in the FAS population. Here, "Number of subjects analysed" signifies the subjects assessed for time to SEGA worsening during the study for each arm, respectively. Here, 99999.9 represents not applicable data because EudraCT system is not accepting "NA" for not available/not applicable data.

End point type	Secondary

End point timeframe:

Baseline, Week 12, Week 24, Week 48 after start of study treatment, and annually thereafter up to End of study

End point values	Everolimus (Core period)	Placebo (Core period)	Everolimus (Extension period)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7[8]	8[9]	40	
Units: Months				
median (confidence interval 95%)	99999.9 (-99999.9 to 99999.9)	99999.9 (-99999.9 to 99999.9)	55.72 (55.72 to 99999.9)	

Notes:

[8] - Median was not achieved as only 7 events of SEGA progression were observed.

[9] - Median was not achieved as only 8 events of SEGA progression were observed.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with skin lesions assessed using Physician's global assessement overall score

End point title	Percentage of subjects with skin lesions assessed using Physician's global assessement overall score

End point description:

Skin lesions included hypomelanotic macules, the shagreen patch, periungual or subungual fibromas, facial angiofibromas and/or forehead plaques. Response was evaluated using the Physician’s Global Assessment of Clinical Condition (PGA) on a 7-point scale: Grade 0 = complete clinical response, indicated absence of disease, Grade 1, 2, and 3 = partial response, indicated improvements of ≥ 50% but < 100%, Grade 4, 5 = stable disease, indicated some or no improvements of 25% - < 50% and 6 = progressive disease, indicated worse than at baseline evaluation by > 25%. Response rate was determined for subjects with ≥ 1 skin lesion at baseline, defined as the percentage of subjects with overall status as complete clinical response or partial response. The analysis was performed in the FAS population. Here, "Number of subjects analysed" signifies the subjects assessed for skin lesion response during the study for each arm, respectively.

End point type	Secondary

End point timeframe:

Start at Week 12 and every 12 weeks thereafter up to End of study

End point values	Everolimus (Core period)	Placebo (Core period)	Everolimus (Extension period)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	38	105	
Units: Percentage of subjects				
median (confidence interval 95%)	41.7 (30.2 to 53.9)	10.5 (2.9 to 24.8)	58.1 (48.1 to 67.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of skin lesion response

End point title	Duration of skin lesion response[10]

End point description:

Duration of skin lesion response was defined as the time from the first skin lesion response until the first skin lesion progression, defined as worsening of lesion by > 25% or more from baseline. The analysis was performed in the FAS population. Here, "Number of subjects analysed" signifies the subjects assessed for skin lesion response during the study for each arm, respectively. Here, 99999.9 represents not applicable data becasue EudraCT system is not accepting "NA" for not available/not applicable data.

End point type	Secondary

End point timeframe:

Start at Week 12 and every 12 weeks thereafter up to End of study

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The end point was planned to evaluate the active treatment (everolimus) arms only.

End point values	Everolimus (Core period)	Everolimus (Extension period)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30[11]	61[12]		
Units: Months				
median (confidence interval 95%)	99999.9 (-99999.9 to 99999.9)	99999.9 (-99999.9 to 99999.9)		

Notes:

[11] - Median was not achieved as no case of skin lesion was observed.

[12] - Median was not achieved as no case of skin lesion was observed.

Statistical analyses

No statistical analyses for this end point

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

End point title	Everolimus blood concentration (C2h) at 2 hours post dose[13]

End point description:

The subjects were assessed for everolimus blood concentration at 2 hours time point after dose administration on the same day, if the subject did not vomit between previous dose and blood sample collection. Tandem liquid chromatography-mass spectrometry method was used for evaluation. C2h values were categorized as < 20 ng/mL, 20-50 ng/mL, and > 50 ng/mL, concentrations below the lower

limit of quantification were entered as 0 ng/mL. The analysis was performed in the Safety Set population (Only evaluable PK Samples), defined as subjects who received at least one dose of the double-blind study drug, with a valid post baseline assessment. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively. Here, the value 99999.9 in the field represents not available estimable. Here, 99999.9 represents not applicable data becasue EudraCT system is not accepting "NA" for not available/not applicable data.

End point type	Secondary

End point timeframe:

Pre-dose, 1-3 hours (Post dose)

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The end point was planned to evaluate the active treatment (everolimus) arms only.

End point values	Everolimus (Core period)	Everolimus (Extension period)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	111		
Units: Nanogram(s)/millilitre				
arithmetic mean (standard deviation)				
Week 6 (n= 37, 47)	27.52 (± 15.24)	27.74 (± 16.202)		
Week 24 (n= 11, 13)	38.7 (± 15.76)	39.25 (± 14.662)		
Week 48 (n= 1, 3)	23.2 (± 99999.9)	49.73 (± 28.884)		
Week 96 (n= 0, 6)	99999.9 (± 99999.9)	31.63 (± 21.902)		
Week 144 (n= 0, 6)	99999.9 (± 99999.9)	26.33 (± 11.908)		
Week 240 (n= 0, 0)	99999.9 (± 99999.9)	99999.9 (± 99999.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Everolimus trough concentrations (Cmin) at 24 hours after last dose

End point title	Everolimus trough concentrations (Cmin) at 24 hours after last dose[14]

End point description:

The subjects were assessed for everolimus trough concentration (Cmin) at 24 hours time point after previous dose administration, at a steady state following 5 days of consistent dosing, if the subject did not vomit within 4 hours of previous dose. Tandem liquid chromatography-mass spectrometry method was used for evaluation. Cmin values were categorized as <5 ng/mL, 5-10 ng/mL, and >10 ng/mL, concentrations below the lower limit of quantification were entered as 0 ng/mL. The analysis was performed in the Safety Set population. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.Here, 99999.9 represents not applicable data becasue EudraCT system is not accepting "NA" for not available/not applicable data.

End point type	Secondary

End point timeframe:

Pre-dose, 20-28 hours (Post-dose)

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The end point was planned to evaluate the active treatment (everolimus) arms only.

End point values	Everolimus (Core period)	Everolimus (Extension period)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	111		
Units: Nanogram(s)/millilitre				
arithmetic mean (standard deviation)				
Week 6 (n= 64, 94)	5.8 (± 3.68)	6.09 (± 3.708)		
Week 24 (n= 64, 89)	6.59 (± 3.43)	6.86 (± 3.504)		
Week 48 (n= 23, 86)	7.28 (± 3.11)	7.07 (± 3.214)		
Week 72 (n= 4, 92)	6.08 (± 2.19)	7.25 (± 3.66)		
Week 96 (n= 0, 83)	99999.9 (± 99999.9)	7.09 (± 3.697)		
Week 144 (n= 0, 69)	99999.9 (± 99999.9)	7.28 (± 3.35)		
Week 240 (n= 0, 13)	99999.9 (± 99999.9)	5.85 (± 2.507)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with renal impairment during core period

End point title	Percentage of subjects with renal impairment during core period

End point description:

Renal function was assessed using glomerular filtration rate (GFR) based on age measure; Modification of Diet in Renal Disease (MDRD) formula for subjects aged 18 years or older, defined as GFR equal to 32788*(serum creatinine (micromol/L)^-1.154)*(age^-0.203)*(0.742, if female)*(1.210, if black), and Schwartz formula for subjects less than 18 years defined as GFR equal to 0.41*height (cm)/ Serum creatinine (mg/dL). Subjects with severe renal impairment defined as GFR < 30 mL/min/1.73 m^2 and subjects with National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) grade 3/4 serum creatinine were reported. The analysis was performed in the SAF population. Here, "Number of subjects analysed" signifies the subjects assessed for renal function during the study for each arm, respectively.

End point type	Secondary

End point timeframe:

Day 1 up to 28 days after end of treatment (Core period)

End point values	Everolimus (Core period)	Placebo (Core period)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	39		
Units: Percentage of subjects				
number (not applicable)				
Grade 3 or 4	0	0		
Grade 1 or 2	3.8	0		
Grade 0	96.2	100		

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 Subject First Visit (FSFV) until Last Subject Last Visit (LSLV). All adverse events reported in this record are from date of First Subject First Treatment until LSLV.

Adverse event reporting additional description:

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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Everolimus (Core + Extension period)

Reporting group description:

Subjects who recieved Everolimu both in core and extension period.

Reporting group title	Placebo (Core) + Everolimus (Extention)

Reporting group description:

All patietns who recieved placebo in core, entered the open-lable extension to recieve everolimus.

Reporting group title	Placebo (Core period, No extension)

Reporting group description:

Subects who recieved placebo in core , did not enter the extnesion period of open-label everolimus

Serious adverse events	Everolimus (Core + Extension period)	Placebo (Core) + Everolimus (Extention)	Placebo (Core period, No extension)
Total subjects affected by serious adverse events			
subjects affected / exposed	33 / 78 (42.31%)	17 / 33 (51.52%)	3 / 6 (50.00%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Raynaud's phenomenon			
subjects affected / exposed	0 / 78 (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
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	3 / 78 (3.85%)	2 / 33 (6.06%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	5 / 7	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			

Hypersensitivity			
subjects affected / exposed	1 / 78 (1.28%)	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
Respiratory, thoracic and mediastinal disorders			
Asphyxia			
subjects affected / exposed	0 / 78 (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 / 1	0 / 0
Pneumonia aspiration			
subjects affected / exposed	1 / 78 (1.28%)	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	1 / 78 (1.28%)	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
Pulmonary pneumatocele			
subjects affected / exposed	0 / 78 (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
Tonsillar hypertrophy			
subjects affected / exposed	1 / 78 (1.28%)	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
Psychiatric disorders			
Affective disorder			
subjects affected / exposed	1 / 78 (1.28%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Agitation			
subjects affected / exposed	1 / 78 (1.28%)	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 alkaline phosphatase increased			
subjects affected / exposed	0 / 78 (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
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 78 (1.28%)	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
Foreign body aspiration			
subjects affected / exposed	1 / 78 (1.28%)	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
Procedural pain			
subjects affected / exposed	1 / 78 (1.28%)	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			
Ataxia			
subjects affected / exposed	1 / 78 (1.28%)	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
Complex partial seizures			
subjects affected / exposed	1 / 78 (1.28%)	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	4 / 78 (5.13%)	1 / 33 (3.03%)	2 / 6 (33.33%)
occurrences causally related to treatment / all	0 / 6	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drooling			

subjects affected / exposed	1 / 78 (1.28%)	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	2 / 78 (2.56%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile convulsion			
subjects affected / exposed	1 / 78 (1.28%)	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
Grand mal convulsion			
subjects affected / exposed	1 / 78 (1.28%)	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
Headache			
subjects affected / exposed	0 / 78 (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
Partial seizures			
subjects affected / exposed	1 / 78 (1.28%)	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
Status epilepticus			
subjects affected / exposed	2 / 78 (2.56%)	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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 78 (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
Lymphadenopathy			

subjects affected / exposed	0 / 78 (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
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 78 (1.28%)	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
Dysphagia			
subjects affected / exposed	1 / 78 (1.28%)	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
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 78 (1.28%)	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
Large intestinal ulcer			
subjects affected / exposed	0 / 78 (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
Mouth ulceration			
subjects affected / exposed	0 / 78 (0.00%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	1 / 78 (1.28%)	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
Umbilical hernia			
subjects affected / exposed	1 / 78 (1.28%)	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
Vomiting			

subjects affected / exposed	1 / 78 (1.28%)	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
Renal and urinary disorders			
Focal segmental glomerulosclerosis			
subjects affected / exposed	1 / 78 (1.28%)	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
Musculoskeletal and connective tissue disorders			
Patellofemoral pain syndrome			
subjects affected / exposed	1 / 78 (1.28%)	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
Temporomandibular joint syndrome			
subjects affected / exposed	0 / 78 (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
Tendon disorder			
subjects affected / exposed	1 / 78 (1.28%)	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			
Acinetobacter bacteraemia			
subjects affected / exposed	0 / 78 (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
Adenovirus infection			
subjects affected / exposed	2 / 78 (2.56%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	2 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	3 / 78 (3.85%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Bronchopneumonia			
subjects affected / exposed	1 / 78 (1.28%)	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
Cellulitis			
subjects affected / exposed	2 / 78 (2.56%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Croup infectious			
subjects affected / exposed	1 / 78 (1.28%)	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
Ear infection bacterial			
subjects affected / exposed	1 / 78 (1.28%)	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
Epstein-Barr virus infection			
subjects affected / exposed	1 / 78 (1.28%)	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
Febrile infection			
subjects affected / exposed	1 / 78 (1.28%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	5 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	4 / 78 (5.13%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	2 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	3 / 78 (3.85%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	4 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal infection			

subjects affected / exposed	1 / 78 (1.28%)	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
Herpes zoster			
subjects affected / exposed	0 / 78 (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
Infected bites			
subjects affected / exposed	1 / 78 (1.28%)	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
Influenza			
subjects affected / exposed	1 / 78 (1.28%)	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
Laryngitis			
subjects affected / exposed	1 / 78 (1.28%)	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
Mastoiditis			
subjects affected / exposed	1 / 78 (1.28%)	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
Meningitis viral			
subjects affected / exposed	0 / 78 (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
Nasopharyngitis			
subjects affected / exposed	1 / 78 (1.28%)	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
Otitis media			

subjects affected / exposed	2 / 78 (2.56%)	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
Parainfluenzae virus infection			
subjects affected / exposed	1 / 78 (1.28%)	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
Pertussis			
subjects affected / exposed	0 / 78 (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	11 / 78 (14.10%)	5 / 33 (15.15%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	9 / 14	2 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection viral			
subjects affected / exposed	1 / 78 (1.28%)	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
Sinusitis			
subjects affected / exposed	0 / 78 (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	1 / 78 (1.28%)	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
Tooth abscess			
subjects affected / exposed	0 / 78 (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
Upper respiratory tract infection			

subjects affected / exposed	2 / 78 (2.56%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 78 (1.28%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	3 / 78 (3.85%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 3	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	1 / 78 (1.28%)	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

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

Non-serious adverse events	Everolimus (Core + Extension period)	Placebo (Core) + Everolimus (Extention)	Placebo (Core period, No extension)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	77 / 78 (98.72%)	33 / 33 (100.00%)	6 / 6 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	3 / 78 (3.85%)	0 / 33 (0.00%)	1 / 6 (16.67%)
occurrences (all)	3	0	1
Vascular disorders			
Hypertension			
subjects affected / exposed	11 / 78 (14.10%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences (all)	11	2	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 78 (0.00%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	0	2	0

Fatigue			
subjects affected / exposed	16 / 78 (20.51%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	17	3	0
Pyrexia			
subjects affected / exposed	25 / 78 (32.05%)	7 / 33 (21.21%)	2 / 6 (33.33%)
occurrences (all)	89	24	3
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	5 / 78 (6.41%)	5 / 33 (15.15%)	0 / 6 (0.00%)
occurrences (all)	9	5	0
Reproductive system and breast disorders			
Amenorrhoea			
subjects affected / exposed	5 / 78 (6.41%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences (all)	5	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	23 / 78 (29.49%)	10 / 33 (30.30%)	1 / 6 (16.67%)
occurrences (all)	46	13	1
Epistaxis			
subjects affected / exposed	4 / 78 (5.13%)	3 / 33 (9.09%)	0 / 6 (0.00%)
occurrences (all)	17	5	0
Nasal congestion			
subjects affected / exposed	2 / 78 (2.56%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	2	3	0
Oropharyngeal pain			
subjects affected / exposed	6 / 78 (7.69%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences (all)	6	2	0
Rhinorrhoea			
subjects affected / exposed	4 / 78 (5.13%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	7	3	0
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	6 / 78 (7.69%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences (all)	6	0	0
Aggression			

subjects affected / exposed	10 / 78 (12.82%)	3 / 33 (9.09%)	0 / 6 (0.00%)
occurrences (all)	13	5	0
Agitation			
subjects affected / exposed	6 / 78 (7.69%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences (all)	6	1	0
Anxiety			
subjects affected / exposed	10 / 78 (12.82%)	3 / 33 (9.09%)	0 / 6 (0.00%)
occurrences (all)	12	3	0
Insomnia			
subjects affected / exposed	11 / 78 (14.10%)	4 / 33 (12.12%)	0 / 6 (0.00%)
occurrences (all)	15	4	0
Irritability			
subjects affected / exposed	5 / 78 (6.41%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences (all)	6	1	0
Obsessive-compulsive disorder			
subjects affected / exposed	5 / 78 (6.41%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences (all)	5	0	0
Sleep disorder			
subjects affected / exposed	1 / 78 (1.28%)	3 / 33 (9.09%)	0 / 6 (0.00%)
occurrences (all)	1	3	0
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	4 / 78 (5.13%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences (all)	4	1	0
Blood cholesterol increased			
subjects affected / exposed	11 / 78 (14.10%)	3 / 33 (9.09%)	1 / 6 (16.67%)
occurrences (all)	15	3	1
Blood fibrinogen decreased			
subjects affected / exposed	5 / 78 (6.41%)	6 / 33 (18.18%)	0 / 6 (0.00%)
occurrences (all)	5	6	0
Blood glucose increased			
subjects affected / exposed	0 / 78 (0.00%)	0 / 33 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Blood lactate dehydrogenase increased			

subjects affected / exposed	6 / 78 (7.69%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences (all)	7	0	0
Blood triglycerides increased			
subjects affected / exposed	7 / 78 (8.97%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences (all)	7	0	0
Carbon dioxide decreased			
subjects affected / exposed	4 / 78 (5.13%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences (all)	4	0	0
Cardiac murmur			
subjects affected / exposed	0 / 78 (0.00%)	0 / 33 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
International normalised ratio increased			
subjects affected / exposed	4 / 78 (5.13%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences (all)	4	1	0
Low density lipoprotein increased			
subjects affected / exposed	6 / 78 (7.69%)	2 / 33 (6.06%)	1 / 6 (16.67%)
occurrences (all)	7	2	1
Neutrophil count decreased			
subjects affected / exposed	6 / 78 (7.69%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences (all)	8	1	0
Weight decreased			
subjects affected / exposed	5 / 78 (6.41%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences (all)	6	1	0
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	3 / 78 (3.85%)	4 / 33 (12.12%)	0 / 6 (0.00%)
occurrences (all)	3	5	0
Excoriation			
subjects affected / exposed	4 / 78 (5.13%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences (all)	5	0	0
Fall			
subjects affected / exposed	2 / 78 (2.56%)	0 / 33 (0.00%)	2 / 6 (33.33%)
occurrences (all)	2	0	2
Hand fracture			

subjects affected / exposed	0 / 78 (0.00%)	0 / 33 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Laceration			
subjects affected / exposed	2 / 78 (2.56%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	2	3	0
Limb injury			
subjects affected / exposed	2 / 78 (2.56%)	1 / 33 (3.03%)	1 / 6 (16.67%)
occurrences (all)	2	1	1
Lip injury			
subjects affected / exposed	0 / 78 (0.00%)	1 / 33 (3.03%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Nervous system disorders			
Convulsion			
subjects affected / exposed	31 / 78 (39.74%)	13 / 33 (39.39%)	4 / 6 (66.67%)
occurrences (all)	85	19	4
Dizziness			
subjects affected / exposed	6 / 78 (7.69%)	3 / 33 (9.09%)	0 / 6 (0.00%)
occurrences (all)	6	5	0
Epilepsy			
subjects affected / exposed	3 / 78 (3.85%)	2 / 33 (6.06%)	1 / 6 (16.67%)
occurrences (all)	3	2	3
Headache			
subjects affected / exposed	13 / 78 (16.67%)	6 / 33 (18.18%)	1 / 6 (16.67%)
occurrences (all)	20	10	1
Migraine with aura			
subjects affected / exposed	0 / 78 (0.00%)	0 / 33 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 78 (7.69%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences (all)	8	1	0
Neutropenia			
subjects affected / exposed	8 / 78 (10.26%)	3 / 33 (9.09%)	0 / 6 (0.00%)
occurrences (all)	15	6	0
Ear and labyrinth disorders			

Ear pain			
subjects affected / exposed	2 / 78 (2.56%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	4	2	0
Vertigo			
subjects affected / exposed	0 / 78 (0.00%)	0 / 33 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	5 / 78 (6.41%)	0 / 33 (0.00%)	1 / 6 (16.67%)
occurrences (all)	9	0	1
Abdominal pain upper			
subjects affected / exposed	5 / 78 (6.41%)	3 / 33 (9.09%)	0 / 6 (0.00%)
occurrences (all)	6	4	0
Constipation			
subjects affected / exposed	11 / 78 (14.10%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	15	2	0
Dental caries			
subjects affected / exposed	5 / 78 (6.41%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	6	2	0
Diarrhoea			
subjects affected / exposed	21 / 78 (26.92%)	7 / 33 (21.21%)	0 / 6 (0.00%)
occurrences (all)	44	12	0
Enteritis			
subjects affected / exposed	2 / 78 (2.56%)	0 / 33 (0.00%)	1 / 6 (16.67%)
occurrences (all)	6	0	1
Mouth ulceration			
subjects affected / exposed	33 / 78 (42.31%)	6 / 33 (18.18%)	0 / 6 (0.00%)
occurrences (all)	87	32	0
Nausea			
subjects affected / exposed	7 / 78 (8.97%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences (all)	10	1	0
Oral pain			
subjects affected / exposed	4 / 78 (5.13%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences (all)	4	1	0
Stomatitis			

subjects affected / exposed	29 / 78 (37.18%)	21 / 33 (63.64%)	1 / 6 (16.67%)
occurrences (all)	137	49	1
Vomiting			
subjects affected / exposed	24 / 78 (30.77%)	6 / 33 (18.18%)	1 / 6 (16.67%)
occurrences (all)	43	12	2
Toothache			
subjects affected / exposed	1 / 78 (1.28%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	1	2	0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	18 / 78 (23.08%)	4 / 33 (12.12%)	0 / 6 (0.00%)
occurrences (all)	18	5	0
Dermatitis			
subjects affected / exposed	1 / 78 (1.28%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	3	2	0
Dry skin			
subjects affected / exposed	4 / 78 (5.13%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences (all)	5	1	0
Eczema			
subjects affected / exposed	5 / 78 (6.41%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences (all)	5	0	0
Rash			
subjects affected / exposed	12 / 78 (15.38%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	22	2	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 78 (0.00%)	0 / 33 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	6 / 78 (7.69%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences (all)	11	0	0
Infections and infestations			
Abscess			
subjects affected / exposed	0 / 78 (0.00%)	0 / 33 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1

Body tinea			
subjects affected / exposed	0 / 78 (0.00%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Bronchitis			
subjects affected / exposed	14 / 78 (17.95%)	5 / 33 (15.15%)	1 / 6 (16.67%)
occurrences (all)	28	6	2
Cellulitis			
subjects affected / exposed	4 / 78 (5.13%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences (all)	6	0	0
Conjunctivitis			
subjects affected / exposed	7 / 78 (8.97%)	5 / 33 (15.15%)	0 / 6 (0.00%)
occurrences (all)	10	6	0
Croup infectious			
subjects affected / exposed	4 / 78 (5.13%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences (all)	6	0	0
Ear infection			
subjects affected / exposed	14 / 78 (17.95%)	4 / 33 (12.12%)	0 / 6 (0.00%)
occurrences (all)	22	10	0
Fungal infection			
subjects affected / exposed	0 / 78 (0.00%)	3 / 33 (9.09%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Gastroenteritis			
subjects affected / exposed	4 / 78 (5.13%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	4	2	0
Gastroenteritis viral			
subjects affected / exposed	9 / 78 (11.54%)	4 / 33 (12.12%)	0 / 6 (0.00%)
occurrences (all)	12	8	0
Gastrointestinal infection			
subjects affected / exposed	1 / 78 (1.28%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	1	2	0
Gastrointestinal viral infection			
subjects affected / exposed	4 / 78 (5.13%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences (all)	4	1	0
Influenza			
subjects affected / exposed	6 / 78 (7.69%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	8	2	0

Laryngitis			
subjects affected / exposed	4 / 78 (5.13%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences (all)	6	0	0
Nasopharyngitis			
subjects affected / exposed	30 / 78 (38.46%)	15 / 33 (45.45%)	1 / 6 (16.67%)
occurrences (all)	59	21	1
Oral candidiasis			
subjects affected / exposed	2 / 78 (2.56%)	0 / 33 (0.00%)	1 / 6 (16.67%)
occurrences (all)	3	0	3
Otitis media			
subjects affected / exposed	16 / 78 (20.51%)	5 / 33 (15.15%)	0 / 6 (0.00%)
occurrences (all)	31	9	0
Pharyngitis			
subjects affected / exposed	12 / 78 (15.38%)	7 / 33 (21.21%)	0 / 6 (0.00%)
occurrences (all)	39	22	0
Pharyngitis streptococcal			
subjects affected / exposed	15 / 78 (19.23%)	2 / 33 (6.06%)	1 / 6 (16.67%)
occurrences (all)	24	4	1
Pneumonia			
subjects affected / exposed	12 / 78 (15.38%)	3 / 33 (9.09%)	1 / 6 (16.67%)
occurrences (all)	16	3	1
Respiratory tract infection			
subjects affected / exposed	6 / 78 (7.69%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences (all)	9	1	0
Respiratory tract infection viral			
subjects affected / exposed	7 / 78 (8.97%)	3 / 33 (9.09%)	0 / 6 (0.00%)
occurrences (all)	17	4	0
Rhinitis			
subjects affected / exposed	8 / 78 (10.26%)	2 / 33 (6.06%)	0 / 6 (0.00%)
occurrences (all)	10	3	0
Sinusitis			
subjects affected / exposed	17 / 78 (21.79%)	4 / 33 (12.12%)	1 / 6 (16.67%)
occurrences (all)	35	8	1
Tracheitis			
subjects affected / exposed	0 / 78 (0.00%)	0 / 33 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1

Upper respiratory tract infection			
subjects affected / exposed	23 / 78 (29.49%)	7 / 33 (21.21%)	3 / 6 (50.00%)
occurrences (all)	35	13	3
Urinary tract infection			
subjects affected / exposed	7 / 78 (8.97%)	1 / 33 (3.03%)	0 / 6 (0.00%)
occurrences (all)	13	4	0
Varicella			
subjects affected / exposed	4 / 78 (5.13%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences (all)	4	0	0
Viral infection			
subjects affected / exposed	6 / 78 (7.69%)	3 / 33 (9.09%)	0 / 6 (0.00%)
occurrences (all)	9	3	0
Vulvovaginal mycotic infection			
subjects affected / exposed	1 / 78 (1.28%)	1 / 33 (3.03%)	1 / 6 (16.67%)
occurrences (all)	1	1	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	12 / 78 (15.38%)	6 / 33 (18.18%)	0 / 6 (0.00%)
occurrences (all)	16	7	0
Dehydration			
subjects affected / exposed	2 / 78 (2.56%)	1 / 33 (3.03%)	2 / 6 (33.33%)
occurrences (all)	2	1	2
Hypercholesterolaemia			
subjects affected / exposed	11 / 78 (14.10%)	3 / 33 (9.09%)	0 / 6 (0.00%)
occurrences (all)	12	3	0
Hyperlipidaemia			
subjects affected / exposed	6 / 78 (7.69%)	0 / 33 (0.00%)	0 / 6 (0.00%)
occurrences (all)	6	0	0
Hypertriglyceridaemia			
subjects affected / exposed	4 / 78 (5.13%)	2 / 33 (6.06%)	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
11 August 2009	The requirement of target lesion volume increase above the baseline value for defining progression was added. The exclusion criterion of prior brain surgery was removed, and renal disease was allowed. Skin lesion response scans were allowed to carry out in 12 weeks after initial response and the screening period was increased from 14 to 21 days
02 April 2010	- Target everolimus concentration range was modified from 10-15 ng/mL to 5-15 ng/mL, two additional dose levels (10.67 mg/m^2 and 14.22 mg/m^2) were added. - Stricter guidance with respect to changes in endocrine hormone levels and hepatitis virus screening was implemented. - The screening period for the study was extended from 21 to 28 days. - Added endocrine blood testing (testosterone, LH, FSH and Estradiol) at screening and subsequent timepoints accorindg to age an gender - Added Tanner staging to assess sexual maturation at screening and subsequent timepoints accorinding to age
11 January 2011	Evaluation of any potential effects of everolimus on growth and development in the pediatric population was allowed. The definition and safety recommendations concerning hepatitis B virus (HBV) reactivation and hepatitis C virus (HCV) flare were modified.
23 February 2011	All subjects have endocrine testing at baseline or at their next scheduled visit (if no prior endocrine testing had been done). Endocrine blood sampling was completed annually until the subject's 10th birthday and every 12 weeks thereafter.
05 March 2012	As part of this amendment, a full pharmacokinetic (PK) profile was collected from subjects currently active in the study. New PK collection time-points were added.
22 August 2012	- 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. - Added completion of hormone evaluations when amenorrhea is seen between scheduled assessments. - Revised 2 tables: - Urine pregnancy testing frequency increased from every 12 weeks to every 4 weeks. - Serum pregnancy test added to End of Treatment evaluation. - Additional menstrual history and pregnancy history information collected. Will conduct monthly monitoring of menstrual status. - Added collection of biological parental height to assist us in the evaluation of patient’s growth and development. - Section revised to include - Urine pregnancy testing frequency increased from every 12 weeks to every 4 weeks. Serum pregnancy test added to End of Treatment evaluation. - Parental height subsection added. Data will be used to evaluation patient’s growth and development. - Revised endocrine testing section to include reproductive history. Additional medical information on reproductive history will be collected. - Additional safety language for pregnancies added - Added data collection language regarding the results from at home urine pregnancy to be recorded on patient diaries for source documentation only.

15 January 2013	- In the section, Amendment (date 22-Aug-2012), Changes to the protocol, the following paragraph is deleted: "This amendment is required for patient safety (i.e. necessary to eliminate immediate hazards to the trial patients International Conference on Harmonization GCP 3.3.8). Therefore it will be implemented prior to IRB/IEC approval, but will be sent for approval as well." - In the section, Amendment (date 22-Aug-2012), Changes to the protocol, the following paragraph is added: "The changes described in this amended protocol require IRB/EC 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."

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, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.novfor complete trial results.

Notes: