Clinical trial results:
A three-arm, randomized, double-blind, placebo-controlled study of the efficacy and safety of two trough-ranges of everolimus as adjunctive therapy in patients with tuberous sclerosis complex (TSC) who have refractory partial-onset seizures - final study closure analysis.

Summary

EudraCT number	2011-000860-90
Trial protocol	ES IT NL DE HU GB BE GR DK IE
Global end of trial date	25 October 2017

Results information

Result version number	v1 (current)
This version publication date	11 May 2018
First version publication date	11 May 2018

Trial information

Trial identification

Sponsor protocol code	CRAD001M2304

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01713946
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma, AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma, AG, 41 613241111, novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma, AG, 41 613241111, novartis.email@novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000019-PIP08-12
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	25 October 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 October 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to compare the reduction in in frequency of partial-onset seizures on each of two trough ranges of everolimus (3 to 7 ng/mL and 9 to15 ng/mL) versus placebo in patients with TSC who were taking one to three antiepileptic drugs (AEDs). Secondary objectives included comparison of the ability to completely suppress TSC-associated seizures, the proportion of patients with ≥ 25% reduction from Baseline in average weekly TSC-associated seizure frequency, distribution of reduction from Baseline in seizure frequency, seizure-free days, treatment duration, and quality of life (QoL).

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	29 April 2013
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	Argentina: 3
Country: Number of subjects enrolled	Australia: 14
Country: Number of subjects enrolled	Belgium: 14
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	Colombia: 11
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	Germany: 23
Country: Number of subjects enrolled	Greece: 3
Country: Number of subjects enrolled	Hungary: 4
Country: Number of subjects enrolled	Ireland: 1
Country: Number of subjects enrolled	Italy: 17
Country: Number of subjects enrolled	Japan: 35
Country: Number of subjects enrolled	Korea, Republic of: 12
Country: Number of subjects enrolled	Mexico: 8
Country: Number of subjects enrolled	Netherlands: 5
Country: Number of subjects enrolled	Norway: 4

Country: Number of subjects enrolled	Poland: 6
Country: Number of subjects enrolled	Russian Federation: 24
Country: Number of subjects enrolled	Spain: 17
Country: Number of subjects enrolled	Taiwan: 20
Country: Number of subjects enrolled	Thailand: 11
Country: Number of subjects enrolled	Turkey: 30
Country: Number of subjects enrolled	United Kingdom: 23
Country: Number of subjects enrolled	United States: 63
Worldwide total number of subjects	366
EEA total number of subjects	129

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)	3
Children (2-11 years)	215
Adolescents (12-17 years)	82
Adults (18-64 years)	66
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

355 patients were planned to be enrolled and a total of 366 patients were randomized: 117 to the everolimus targeted low-trough arm (LT), 130 to the everolimus targeted high-trough (HT) arm, and 119 to treatment with placebo.

Pre-assignment

Screening details:

The study consisted of 4 phases. Baseline phase: [From Screening Week -8 (V1) to randomization at Week 0 (V2)], Core phase [from randomization at Week 0 (V2) to Week 18 (V11)], Extension phase [from Week 18 (V11) to 48 weeks after the last patient had completed the core phase] and Post Extension phase [from end of Extension phase to end of study].

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Everolimus LT target of 3 to 7 ng/mL

Arm description:

Participants randomized to receive everolimus dispersible tablets for oral suspension with titration to a low trough (LT) range of 3 to 7 ng/mL

Arm type	Experimental
Investigational medicinal product name	Antiepileptic drug
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

No more than 3 Antiepileptic drugs could be taken with the study drug or placebo.

Investigational medicinal product name	Everolimus
Investigational medicinal product code	RAD001
Other name	
Pharmaceutical forms	Dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

Everolimus was administered orally on a once-daily basis to attain target trough concentrations of 3-7 ng/mL or 9-15 ng/mL during the first 18 weeks (Core phase), 3-15 ng/mL during the Extension phase and 5-15 ng/mL during the Post-extension phase.

Arm title	Everolimus HT target of 9 to 15 ng/mL

Arm description:

Participants randomized to receive everolimus dispersible tablets for oral suspension with titration to a high trough (HT) range of 9 to 15 ng/mL

Arm type	Experimental

Investigational medicinal product name	Antiepileptic drug
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

No more than 3 Antiepileptic drugs could be taken with the study drug or placebo.

Investigational medicinal product name	Everolimus
Investigational medicinal product code	RAD001
Other name	
Pharmaceutical forms	Dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

Everolimus was administered orally on a once-daily basis to attain target trough concentrations of 3-7 ng/mL or 9-15 ng/mL during the first 18 weeks (Core phase), 3-15 ng/mL during the Extension phase and 5-15 ng/mL during the Post-extension phase.

Arm title	Placebo

Arm description:

Participants randomized to receive placebo dispersible tablets for oral suspension at study start (114 of them switched to everolimus in Extension)

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

Dosage and administration details:

Everolimus was administered orally on a once-daily basis to attain target trough concentrations of 3-7 ng/mL or 9-15 ng/mL during the first 18 weeks (Core phase), 3-15 ng/mL during the Extension phase and 5-15 ng/mL during the Post-extension phase.

Investigational medicinal product name	Antiepileptic drug
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

No more than 3 Antiepileptic drugs could be taken with the study drug or placebo.

Number of subjects in period 1	Everolimus LT target of 3 to 7 ng/mL	Everolimus HT target of 9 to 15 ng/mL	Placebo
Started	117	130	119
Completed Core Phase	110	122	114
Continued in Ext. Phase	110	119	114
Completed Ext. Phase	79	92	81
Continued in Post-Ext. Phase	78	90	81
Completed Post-Ext Phase	74	85	75
Did not continue in Ext Phase	0 [1]	3 [2]	0 [3]
Did not cont. in Post-Ext Phase	1 [4]	2 [5]	0 [6]

Completed	74	85	75
Not completed	43	45	44
Adverse event, serious fatal	-	2	2
Consent withdrawn by subject	12	12	8
Did not continue in Ext	-	3	-
Adverse event, non-fatal	19	14	13
Administrative problems	1	-	-
Did not continue in Post-Ext. Phase	1	2	-
Lost to follow-up	-	-	1
Did not switch from Pbo to Everolimus Ext.	-	-	5
Lack of efficacy	8	8	14
Protocol deviation	2	4	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Correct

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Correct

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Correct

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Correct

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Correct

[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Correct

Baseline characteristics

Reporting groups	
Reporting group title	Everolimus LT target of 3 to 7 ng/mL
Reporting group description:	
Participants randomized to receive everolimus dispersible tablets for oral suspension with titration to a low trough (LT) range of 3 to 7 ng/mL	
Reporting group title	Everolimus HT target of 9 to 15 ng/mL
Reporting group description:	
Participants randomized to receive everolimus dispersible tablets for oral suspension with titration to a high trough (HT) range of 9 to 15 ng/mL	
Reporting group title	Placebo
Reporting group description:	
Participants randomized to receive placebo dispersible tablets for oral suspension at study start (114 of them switched to everolimus in Extension)	

Reporting group values	Everolimus LT target of 3 to 7 ng/mL	Everolimus HT target of 9 to 15 ng/mL	Placebo
Number of subjects	117	130	119
Age, Customized Units: Subjects			
< 6 years|	33	37	34
6 to <12 years|	37	39	37
12 to <18 years|	26	31	25
18 to <65 years|	21	23	23
Age Continuous Units: years			
median	9.72	10.08	10.34
full range (min-max)	2.2 to 56.3	2.3 to 50.5	2.2 to 52.0
Sex: Female, Male Units: Subjects			
Female	53	65	58
Male	64	65	61
Race/Ethnicity, Customized Units: Subjects			
Caucasian|	76	84	77
Asian|	29	31	27
Black|	2	1	1
Native American|	0	1	0
Pacific Islander|	1	0	0
Other|	9	13	14
Weight Units: kg			
arithmetic mean	38.69	40.75	40.50
standard deviation	± 22.802	± 27.267	± 24.923
Height Units: cm			
arithmetic mean	135.65	136.25	135.67
standard deviation	± 26.171	± 28.234	± 27.097
Body surface area			

Units: m^2			
arithmetic mean	1.18	1.20	1.20
standard deviation	± 0.437	± 0.501	± 0.176
Body mass index			
Units: kg/m^2			
arithmetic mean	19.29	19.56	19.55
standard deviation	± 5.283	± 6.233	± 5.689

Reporting group values	Total		
Number of subjects	366		
Age, Customized			
Units: Subjects			
< 6 years|	104		
6 to <12 years|	113		
12 to <18 years|	82		
18 to <65 years|	67		
Age Continuous			
Units: years			
median			
full range (min-max)	-		
Sex: Female, Male			
Units: Subjects			
Female	176		
Male	190		
Race/Ethnicity, Customized			
Units: Subjects			
Caucasian|	237		
Asian|	87		
Black|	4		
Native American|	1		
Pacific Islander|	1		
Other|	36		
Weight			
Units: kg			
arithmetic mean			
standard deviation	-		
Height			
Units: cm			
arithmetic mean			
standard deviation	-		
Body surface area			
Units: m^2			
arithmetic mean			
standard deviation	-		
Body mass index			
Units: kg/m^2			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Everolimus LT target of 3 to 7 ng/mL
Reporting group description:	
Participants randomized to receive everolimus dispersible tablets for oral suspension with titration to a low trough (LT) range of 3 to 7 ng/mL	
Reporting group title	Everolimus HT target of 9 to 15 ng/mL
Reporting group description:	
Participants randomized to receive everolimus dispersible tablets for oral suspension with titration to a high trough (HT) range of 9 to 15 ng/mL	
Reporting group title	Placebo
Reporting group description:	
Participants randomized to receive placebo dispersible tablets for oral suspension at study start (114 of them switched to everolimus in Extension)	
Subject analysis set title	<3 ng/mL
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Observed TN-Cmin concentration during the maintenance of the core phase: <3 ng/mL	
Subject analysis set title	3-7 ng/mL
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Observed TN-Cmin concentration during the maintenance of the core phase:3 - 7 ng/mL	
Subject analysis set title	>7-<9 ng/mL
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Observed TN-Cminconcentration during the maintenance of the core phase: >7 - <9 ng/mL	
Subject analysis set title	9-15 ng/mL
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Observed TN-Cmin concentration during the maintenance of the core phase: 9 - 15 ng/mL	
Subject analysis set title	>15 ng/mL
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Observed TN-Cmin concentration during the maintenance of the core phase: >15 ng/mL	
Subject analysis set title	Valporic acid
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Antiepileptic drug	
Subject analysis set title	Carbamazepine
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Antiepileptic drug	
Subject analysis set title	Cobazam
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
antiepileptic drug	
Subject analysis set title	N-desmethylclobazam
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
antiepileptic drug	

Subject analysis set title	Topiramate
Subject analysis set type	Sub-group analysis
Subject analysis set description: antiepileptic drug	
Subject analysis set title	TRI477
Subject analysis set type	Sub-group analysis
Subject analysis set description: antiepileptic drug	
Subject analysis set title	TRI476
Subject analysis set type	Sub-group analysis
Subject analysis set description: antiepileptic drug	
Subject analysis set title	Clonazepam
Subject analysis set type	Sub-group analysis
Subject analysis set description: antiepileptic drug	
Subject analysis set title	Zonisamide
Subject analysis set type	Sub-group analysis
Subject analysis set description: antiepileptic drug	
Subject analysis set title	Phenobarbital
Subject analysis set type	Sub-group analysis
Subject analysis set description: antiepileptic drug	
Subject analysis set title	Phenytoin
Subject analysis set type	Sub-group analysis
Subject analysis set description: antiepileptic drug	
Subject analysis set title	Everolimus Long Term Evaluation
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Participants who were treated with everolimus either in the Core or Extension phases of the study and were evaluated for longer term safety and efficacy.	
Subject analysis set title	Placebo to Everolimus Start Extension
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants who received placebo dispersible tablets for oral suspension at study start and switched to everolimus in Extension	

Primary: Core Phase: European Medicine Agency (EMA): Seizure frequency Response rate

End point title	Core Phase: European Medicine Agency (EMA): Seizure frequency Response rate
End point description: Comparison of response rates in the everolimus low-trough treatment arm (3-7 ng/mL), high-trough treatment arm (9-15 ng/mL) and placebo arm. Response means at least a 50% reduction from baseline in partial-onset seizure frequency during the maintenance period of the core phase.	
End point type	Primary
End point timeframe: Baseline (8-week period before randomization), Week 7 to 18 (12-week maintenance period of the core phase)	

End point values	Everolimus LT target of 3 to 7 ng/mL	Everolimus HT target of 9 to 15 ng/mL	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	117	130	119	
Units: Percentage of responders				
number (confidence interval 95%)	28.2 (20.3 to 37.3)	40.0 (31.5 to 49.0)	15.1 (9.2 to 22.8)	

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	Everolimus LT target of 3 to 7 ng/mL v Placebo
Number of subjects included in analysis	236
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.008
Method	Bonferroni-Holm
Parameter estimate	Odds ratio (OR)
Point estimate	2.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.16
upper limit	4.2

Statistical analysis title	Analysis 2
Comparison groups	Everolimus HT target of 9 to 15 ng/mL v Placebo
Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Bonferroni-Holm
Parameter estimate	Odds ratio (OR)
Point estimate	3.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.1
upper limit	7.32

Primary: Core Phase: Food & Drug Administration (FDA): Percentage reduction from baseline in partial onset-seizure frequency

End point title	Core Phase: Food & Drug Administration (FDA): Percentage reduction from baseline in partial onset-seizure frequency

End point description:

Comparison of median percent reduction from baseline in weekly seizure frequency in the everolimus low-trough treatment arm (3-7 ng/mL), high-trough treatment arm (9-15 ng/mL) and placebo arm during maintenance period of the core phase.

End point type	Primary

End point timeframe:

Baseline (8-week period before randomization), Week 7 to 18 (12-week maintenance period of the core phase)

End point values	Everolimus LT target of 3 to 7 ng/mL	Everolimus HT target of 9 to 15 ng/mL	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	117	130	119	
Units: Percentage				
median (confidence interval 95%)	29.29 (18.82 to 41.88)	39.55 (35.03 to 48.74)	14.86 (0.11 to 21.71)	

Statistical analyses

Statistical analysis title	Analysis 3
Comparison groups	Placebo v Everolimus LT target of 3 to 7 ng/mL
Number of subjects included in analysis	236
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	Bonferroni-Holm
Parameter estimate	Median difference (final values)
Point estimate	15.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.98
upper limit	31.68

Statistical analysis title	Analysis 4
Comparison groups	Everolimus HT target of 9 to 15 ng/mL v Placebo

Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Bonferroni-Holm
Parameter estimate	Median difference (final values)
Point estimate	27.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	16.36
upper limit	43.36

Secondary: Core Phase: Seizure freedom

End point title	Core Phase: Seizure freedom

End point description:

Comparison of seizure freedom (100% reduction in seizure frequency) in the everolimus low-trough treatment arm (3-7 ng/mL), high-trough treatment arm (9-15 ng/mL) and placebo arm during maintenance period of the core phase. Seizure free means a 100% reduction from baseline in partial-onset seizure frequency during maintenance period of the core phase.

End point type	Secondary

End point timeframe:

Baseline (8-week period before randomization), Week 7 to 18 (12-week maintenance period of the core phase)

End point values	Everolimus LT target of 3 to 7 ng/mL	Everolimus HT target of 9 to 15 ng/mL	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	117	130	119	
Units: Percentage of seizure-free participants				
number (confidence interval 95%)	5.1 (1.9 to 10.8)	3.8 (1.3 to 8.7)	0.8 (0.0 to 4.6)	

Statistical analyses

Statistical analysis title	Analysis 5
Comparison groups	Everolimus LT target of 3 to 7 ng/mL v Placebo
Number of subjects included in analysis	236
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	6.55

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	55.73

Statistical analysis title	Analysis 6
Comparison groups	Everolimus HT target of 9 to 15 ng/mL v Placebo
Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	4.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	44.03

Secondary: Core Phase: Percentage of patients with at least a 25% reduction in seizure frequency

End point title	Core Phase: Percentage of patients with at least a 25% reduction in seizure frequency

End point description:

Comparison of percentage of patients with at least ≥ 25% reduction in seizure frequency in the everolimus low-trough treatment arm (3-7 ng/mL), high-trough treatment arm (9-15 ng/mL) and placebo arm during maintenance period of the core phase. At least 25% reduction from baseline in partial-onset seizure frequency during maintenance period of the core phase.

End point type	Secondary

End point timeframe:

Baseline (8-week period before randomization), Week 7 to 18 (12-week maintenance period of the core phase)

End point values	Everolimus LT target of 3 to 7 ng/mL	Everolimus HT target of 9 to 15 ng/mL	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	117	130	119	
Units: Percentage of participants				
number (confidence interval 95%)	52.1 (42.7 to 61.5)	70.0 (61.3 to 77.7)	37.8 (29.1 to 47.2)	

Statistical analyses

Statistical analysis title	Analysis 7
Comparison groups	Everolimus LT target of 3 to 7 ng/mL v Placebo
Number of subjects included in analysis	236
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	1.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.05
upper limit	2.97

Statistical analysis title	Analusis 8
Comparison groups	Everolimus HT target of 9 to 15 ng/mL v Placebo
Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	3.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.25
upper limit	6.48

Secondary: Core phase: Distribution of reduction from Baseline in seizure frequency	
End point title	Core phase: Distribution of reduction from Baseline in seizure frequency

End point description:

Comparison of percentage of patients in six categories of seizure reduction from baseline (≤ -25% (exacerbation); > -25% to < 25% (no change); ≥ 25% to < 50%; ≥ 50% to < 75%; ≥ 75% to < 100%; 100% (seizure-freedom)) in the everolimus low-trough treatment arm (3-7 ng/mL), high-trough treatment arm (9-15 ng/mL) and placebo arm during maintenance period of the core phase

End point type	Secondary

End point timeframe:

Baseline (8-week period before randomization), Week 7 to 18 (12-week maintenance period of the core phase)

End point values	Everolimus LT target of 3 to 7 ng/mL	Everolimus HT target of 9 to 15 ng/mL	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	117	130	119	
Units: Percentage of participants				
number (not applicable)				
100% (seizure free)|	5.1	3.8	0.8	
≥ 75 to <100 (75% responder)|	6.0	15.4	5.0	
≥ 50 to <75 (50% responder)|	17.1	20.8	9.2	
≥ 25 to <50 (25% responder)|	23.9	30.0	22.7	
>-25 to <25 (No change)|	35.0	18.5	41.2	
≤ -25 (Exacerbation)|	12.8	11.5	20.2	
Missing (missing)|	0.0	0.0	0.8	

Statistical analyses

No statistical analyses for this end point

Secondary: Core Phase: Changes from baseline in number of seizure-free days

End point title	Core Phase: Changes from baseline in number of seizure-free days

End point description:

Comparison of seizure-free days relative to baseline in the everolimus low-trough treatment arm (3-7 ng/mL), high-trough treatment arm (9-15 ng/mL) and placebo arm during maintenance period of the core phase

End point type	Secondary

End point timeframe:

Baseline (8-week period before randomization), Week 7 to 18 (12-week maintenance period of the core phase)

End point values	Everolimus LT target of 3 to 7 ng/mL	Everolimus HT target of 9 to 15 ng/mL	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	117	130	119	
Units: Number of seizure-free days -per 28 days				
median (full range (min-max))	2.00 (-23.1 to 27.7)	4.01 (-10.0 to 27.5)	0.47 (-13.4 to 21.8)	

Statistical analyses

Statistical analysis title	Analysis 5
Comparison groups	Everolimus LT target of 3 to 7 ng/mL v Placebo

Number of subjects included in analysis	236
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Mean difference (final values)
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	3.1

Statistical analysis title	Analysis 6
Comparison groups	Everolimus HT target of 9 to 15 ng/mL v Placebo
Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Mean difference (final values)
Point estimate	4.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.5
upper limit	5.9

Secondary: Core phase: Overall summary of time to treatment discontinuation using Kaplan- Meier methodology

End point title	Core phase: Overall summary of time to treatment discontinuation using Kaplan- Meier methodology

End point description:

Comparison of time to treatment discontinuation in the everolimus low-trough treatment arm (3-7 ng/mL), high-trough treatment arm (9-15 ng/mL) and placebo arm during maintenance period of the core phase

End point type	Secondary

End point timeframe:

Week 6, Week 12, Week 18

End point values	Everolimus LT target of 3 to 7 ng/mL	Everolimus HT target of 9 to 15 ng/mL	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	117	130	119	
Units: Percentage event-free prob. estimates				
number (confidence interval 95%)				
Week 6|	97.4 (92.3 to 99.2)	96.2 (91.0 to 98.4)	99.2 (94.2 to 99.9)	

Week 12|	95.7 (90.0 to 98.2)	95.4 (90.0 to 97.9)	97.5 (92.4 to 99.2)	
Week 18|	70.1 (60.9 to 77.5)	71.5 (62.9 to 78.5)	75.6 (66.9 to 82.4)	

Statistical analyses

Statistical analysis title	Analysis 9
Comparison groups	Placebo v Everolimus LT target of 3 to 7 ng/mL
Number of subjects included in analysis	236
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	1.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	2.07

Statistical analysis title	Analysis 10
Comparison groups	Everolimus HT target of 9 to 15 ng/mL v Placebo
Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	1.96

Secondary: Core Phase: Change from baseline of Patient-oriented outcomes (PROs) Quality of Life (QoL) questionnaire: QOLCE - patients <11 years

End point title	Core Phase: Change from baseline of Patient-oriented outcomes (PROs) Quality of Life (QoL) questionnaire: QOLCE - patients <11 years

End point description:

Comparison of quality of life in the everolimus (from 3 age specific questionnaires) low-trough treatment arm (3-7 ng/mL), high-trough treatment arm (9-15 ng/mL) and placebo arm at the end of the core phase. The Quality of Life Childhood Epilepsy (QOLCE) questionnaire, used for patients < 11 years at baseline, was completed by the patient's parent or caregiver. It consists of 16 subscales (13 multi-item scales and 3 single item scales) and one overall quality-of-life score. Scores range from 0-100, with higher scores corresponding to improved QoL.

End point type	Secondary

End point timeframe:
Baseline, Week 18

End point values	Everolimus LT target of 3 to 7 ng/mL	Everolimus HT target of 9 to 15 ng/mL	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	65	69	63	
Units: scores on a scale				
arithmetic mean (standard deviation)	1.2 (± 10.52)	1.2 (± 7.91)	1.3 (± 8.91)	

Statistical analyses

Statistical analysis title	Analysis 11
Comparison groups	Everolimus LT target of 3 to 7 ng/mL v Placebo
Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in least square means
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.4
upper limit	2.1

Statistical analysis title	Analysis 12
Comparison groups	Everolimus HT target of 9 to 15 ng/mL v Placebo
Number of subjects included in analysis	132
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in least square means
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.2
upper limit	4.3

Secondary: Core Phase: Change from baseline of Patient-oriented outcomes (PROs) Quality of Life (QoL) questionnaire: QOLIE-AD-48 - patients >=11 to <18 years

End point title	Core Phase: Change from baseline of Patient-oriented

	outcomes (PROs) Quality of Life (QoL) questionnaire: QOLIE-AD-48 - patients >=11 to <18 years

End point description:

Comparison of quality of life (from 3 age specific questionnaires) in the everolimus low-trough treatment arm (3-7 ng/mL), high-trough treatment arm (9-15 ng/mL) and placebo arm at the end of the core phase. The QOLIE-AD-48 is survey of health-related quality of life for adolescents 11 to 18 years of age with epilepsy. It is completed only by the person who has epilepsy. There are 48 questions in 2 parts about health and daily activities. The first part is about general health and the second part asks about epilepsy and the antiepileptic medications. Higher scores indicate better quality of life.

End point type	Secondary

End point timeframe:

Baseline, Week 18

End point values	Everolimus LT target of 3 to 7 ng/mL	Everolimus HT target of 9 to 15 ng/mL	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	31	38	33	
Units: scores on a scale				
arithmetic mean (standard deviation)	1.8 (± 7.06)	6.0 (± 13.83)	4.9 (± 12.81)	

Statistical analyses

Statistical analysis title	Analysis 13
Comparison groups	Everolimus LT target of 3 to 7 ng/mL v Placebo
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in least square means
Point estimate	-2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.5
upper limit	6.2

Statistical analysis title	Analysis 14
Comparison groups	Everolimus HT target of 9 to 15 ng/mL v Placebo
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in least square means
Point estimate	0.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.8
upper limit	8.6

Secondary: Core Phase: Change from baseline of Patient-oriented outcomes (PROs) Quality of Life (QoL) questionnaire: QOLIE-31-P patients aged >=18 years

End point title	Core Phase: Change from baseline of Patient-oriented outcomes (PROs) Quality of Life (QoL) questionnaire: QOLIE-31-P patients aged >=18 years

End point description:

Comparison of quality of life (from 3 age specific questionnaires) in the everolimus low-trough treatment arm (3-7 ng/mL), high-trough treatment arm (9-15 ng/mL) and placebo arm at the end of the core phase. The Quality of Life in Epilepsy (QOLIE-31) contains seven multi-item scales that tap the following health concepts: emotional well-being, social functioning, energyfatigue, cognitive functioning, seizure worry, medication effects and overall quality of life. A QOLIE-31 overall score is obtained using a weighted average of the multi-term scale scores. The QOLIE-31 also includes a single item that assesses overall health. Higher scores indicate better quality of life.

End point type	Secondary

End point timeframe:

Baseline, Week 18

End point values	Everolimus LT target of 3 to 7 ng/mL	Everolimus HT target of 9 to 15 ng/mL	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	21	23	23	
Units: scores on a scale				
arithmetic mean (standard deviation)	4.9 (± 15.84)	-2.4 (± 17.36)	5.7 (± 17.15)	

Statistical analyses

Statistical analysis title	Analysis 15
Comparison groups	Everolimus LT target of 3 to 7 ng/mL v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in least square means
Point estimate	-2.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.9
upper limit	12.3

Statistical analysis title	Analysis 16
Comparison groups	Everolimus HT target of 9 to 15 ng/mL v Placebo
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in least square means
Point estimate	-7.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22
upper limit	6.6

Secondary: Core phase: Change from Baseline in Vineland-II Adaptive Behavior Composite Score (VABS-ll)

End point title	Core phase: Change from Baseline in Vineland-II Adaptive Behavior Composite Score (VABS-ll)

End point description:

Comparison of adaptive functioning using the VABS-II composite score in the everolimus low-trough treatment arm (3-7 ng/mL), high-trough treatment arm (9-15 ng/mL) and placebo arm. Change from Baseline only includes patients who used the same form at both Baseline & end of Core phase. The Vineland Adaptive Behavior Scales is used to assess adaptive behavior in individuals with ASD as well as other populations. The VABS evaluates adaptive functioning in 4 domains: Communication, Daily Living Skills, Socialization, and Motor Skills (Motor Skills norms are only available for children under 6). Age Equivalent scores & Standard Scores are provided for each domain, & scores across domains can be combined to create an overall Adaptive Behavior Composite score (ABC). The Vineland II assesses an individual's development of personal independence & social responsibility by gathering information about day-to-day activities necessary to take care of oneself & to get along with others.

End point type	Secondary

End point timeframe:

Baseline, 18 weeks

End point values	Everolimus LT target of 3 to 7 ng/mL	Everolimus HT target of 9 to 15 ng/mL	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	75	93	76	
Units: scores on a scale				
arithmetic mean (standard deviation)	-0.11 (± 7.806)	-0.13 (± 6.355)	0.61 (± 5.383)	

Statistical analyses

No statistical analyses for this end point

Secondary: Long Term Evaluation: Change from Baseline in Vineland-II Adaptive Behavior Composite Score – Patients in countries where Vineland-II was implemented

End point title	Long Term Evaluation: Change from Baseline in Vineland-II Adaptive Behavior Composite Score – Patients in countries where Vineland-II was implemented

End point description:

Comparison of adaptive functioning using the VABS-II composite score in the everolimus low-trough treatment arm (3-7 ng/mL), high-trough treatment arm (9-15 ng/mL) and placebo arm. Change from Baseline only includes patients who used the same form at both Baseline & end of Core phase. The Vineland Adaptive Behavior Scales is used to assess adaptive behavior in individuals with ASD as well as other populations. The VABS evaluates adaptive functioning in 4 domains: Communication, Daily Living Skills, Socialization, and Motor Skills (Motor Skills norms are only available for children under 6). Age Equivalent scores & Standard Scores are provided for each domain, & scores across domains can be combined to create an overall Adaptive Behavior Composite score (ABC). The Vineland II assesses an individual's development of personal independence & social responsibility by gathering information about day-to-day activities necessary to take care of oneself & to get along with others.

End point type	Secondary

End point timeframe:

Weeks 18, 42, 66 and 90

End point values	Everolimus Long Term Evaluation			
Subject group type	Subject analysis set			
Number of subjects analysed	239			
Units: scores on a scale				
arithmetic mean (standard deviation)				
Week 18 (n = 62)|	-0.42 (± 6.261)			
Week 42 (n = 54)|	-0.63 (± 5.349)			
Week 66 (n = 48)|	-1.19 (± 5.712)			
Week 90 (n = 34)|	-1.35 (± 6.624)			

Statistical analyses

No statistical analyses for this end point

Secondary: Core phase: Change from Baseline in Wechsler Nonverbal Composite Score

End point title	Core phase: Change from Baseline in Wechsler Nonverbal Composite Score

End point description:

Comparison of adaptive functioning using the Westchester Nonverbal Composite score (WNV) composite score in the everolimus low-trough treatment arm (3-7 ng/mL), high-trough treatment arm (9-15 ng/mL) and placebo arm. WNV is an individual nonverbal assessment of general cognitive ability for ages 4 years and 0 months to 21 years and 11 months. The test assesses Nonverbal IQ in a robust, yet relatively quick and easy-to-administer format. The inclusion of pictorial directions is unique and makes

the test an option if English proficiency of the examinee is a concern. The test materials are well put together, colorful, and engaging.

End point type	Secondary

End point timeframe:

Baseline, Week 18

End point values	Everolimus LT target of 3 to 7 ng/mL	Everolimus HT target of 9 to 15 ng/mL	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	89	94	85	
Units: scores on a scale				
arithmetic mean (standard deviation)	0.03 (± 0.655)	-0.04 (± 1.483)	0.08 (± 0.718)	

Statistical analyses

No statistical analyses for this end point

Secondary: Long Term Evaluation: Change from Baseline in Wechsler Nonverbal Composite Score

End point title	Long Term Evaluation: Change from Baseline in Wechsler Nonverbal Composite Score

End point description:

Change from start of everolimus of adaptive functioning using the WNV composite score for all everolimus treated patients. This questionnaire was completed only by patients aged between 4 to 21 years old at randomization. WNV is an individual nonverbal assessment of general cognitive ability for ages 4 years and 0 months to 21 years and 11 months. The test assesses Nonverbal IQ in a robust, yet relatively quick and easy-to-administer format. The inclusion of pictorial directions is unique and makes the test an option if English proficiency of the examinee is a concern. The test materials are well put together, colorful, and engaging.

End point type	Secondary

End point timeframe:

Weeks 18, 42, 66 and 90

End point values	Everolimus Long Term Evaluation			
Subject group type	Subject analysis set			
Number of subjects analysed	265			
Units: scores on a scale				
arithmetic mean (standard deviation)				
Week 18 (n = 148)|	0.07 (± 1.063)			
Week 42 (n = 131)|	0.33 (± 1.311)			
Week 66 (n = 96)|	0.34 (± 1.316)			
Week 90 (n= 76)|	0.35 (± 1.108)			

Statistical analyses

No statistical analyses for this end point

Secondary: Core Phase: Response rate and percentage reduction from Baseline in seizure frequency by time normalized minimum concentration

End point title	Core Phase: Response rate and percentage reduction from Baseline in seizure frequency by time normalized minimum concentration

End point description:

Comparison of response rate and percentage reduction from Baseline in seizure frequency for 5 categories of time-normalized minimum concentration (Cmin, TN) (< 3 ng/mL; 3-7 ng/mL; >7-<9 ng/mL; 9-15 ng/mL; >15 ng/mL)

End point type	Secondary

End point timeframe:

Baseline (8-week period before randomization), Week 7 to 18 (12-week maintenance period of the core phase)

End point values	<3 ng/mL	3-7 ng/mL	>7-<9 ng/mL	9-15 ng/mL
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	14	147	52	30
Units: Percentage				
median (confidence interval 95%)				
Response rate|	14.3 (1.8 to 42.8)	29.9 (22.7 to 38.0)	44.2 (30.5 to 58.7)	50.0 (31.3 to 68.7)
Median percentage reduction from Baseline|	20.55 (-8.45 to 35.39)	35.56 (24.43 to 41.88)	39.72 (28.02 to 62.79)	47.69 (36.46 to 66.32)

End point values	>15 ng/mL			
Subject group type	Subject analysis set			
Number of subjects analysed	2			
Units: Percentage				
median (confidence interval 95%)				
Response rate|	50.0 (1.3 to 98.7)			
Median percentage reduction from Baseline|	61.56 (42.73 to 80.38)			

Statistical analyses

No statistical analyses for this end point

Secondary: Long Term evaluation: Relationship between seizure frequency and time-normalized everolimus concentration at trough (Cmin,TN) - repeated measures analysis

End point title	Long Term evaluation: Relationship between seizure frequency and time-normalized everolimus concentration at trough (Cmin,TN) - repeated measures analysis

End point description:

Percentage reduction in post-Baseline seizure frequency for a 2-fold increase in TN Cmin, for a 0.5-fold lower Baseline seizure frequency, for a 12 weeks more on treatment based on a linear mixed model considering fixed intervals: absolute seizure frequency in log scale as dependent variable, log (Cmin,TN) (ng/mL) and log (baseline seizure frequency) as fixed effect continuous covariates, and number of days between start of everolimus and start of fixed interval as a continuous covariate with a random effect on the slope. Patient as random effect.

End point type	Secondary

End point timeframe:

Baseline, Week 42, 12 weeks more on treatment

End point values	Everolimus Long Term Evaluation			
Subject group type	Subject analysis set			
Number of subjects analysed	358			
Units: Percentage				
number (confidence interval 95%)				
2-fold increase in log Cmin, TN|	8.93 (6.87 to 10.95)			
0.5-fold lower baseline seizure frequency|	48.82 (46.37 to 51.15)			
12 weeks more on treatment|	6.42 (4.53 to 8.27)			

Statistical analyses

No statistical analyses for this end point

Secondary: Core Phase: Impact of everolimus on anti-epileptic drugs (AEDs) concentrations

End point title	Core Phase: Impact of everolimus on anti-epileptic drugs (AEDs) concentrations

End point description:

Impact of everolimus on AED concentrations at trough

End point type	Secondary

End point timeframe:

Baseline, Weeks 1 & 3

End point values	Valporic acid	Carbamazepine	Cobazam	N-desmethylclobazam
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	86	34	37	37
Units: ng/mL				
geometric mean (confidence interval 90%)				
Geo-mean ratio	0.962 (0.913 to 1.014)	1.108 (1.016 to 1.208)	1.093 (1.037 to 1.153)	1.071 (1.017 to 1.127)

End point values	Topiramate	TRI477	TRI476	Clonazepam
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	34	31	31	17
Units: ng/mL				
geometric mean (confidence interval 90%)				
Geo-mean ratio	0.983 (0.872 to 1.108)	1.086 (0.913 to 1.291)	1.194 (0.936 to 1.523)	1.065 (0.974 to 1.163)

End point values	Zonisamide	Phenobarbital	Phenytoin	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	12	11	7	
Units: ng/mL				
geometric mean (confidence interval 90%)				
Geo-mean ratio	1.028 (0.971 to 1.089)	0.957 (0.886 to 1.034)	1.020 (0.874 to 1.190)	

Statistical analyses

No statistical analyses for this end point

Secondary: Long Term Evaluation: Percentage reduction from baseline in seizure frequency by time window

End point title	Long Term Evaluation: Percentage reduction from baseline in seizure frequency by time window

End point description:

Percentage reduction from baseline in seizure frequency and response rate by time window

End point type	Secondary

End point timeframe:

Baseline (8-week period before start of everolimus), Week 7 to 18, Week 19 to 30, and 12 weeks thereafter until end of extension phase

End point values	Everolimus Long Term Evaluation			
Subject group type	Subject analysis set			
Number of subjects analysed	361			
Units: Percentage				
median (confidence interval 95%)				
Week 18 (n = 352)|	31.65 (28.51 to 36.09)			
Week 30 (n = 335)|	35.74 (29.37 to 39.06)			
Week 42 (n = 320)|	42.86 (34.44 to 48.15)			
Week 54 (n = 299)|	46.05 (39.93 to 53.61)			
Week 66 (n = 282)|	49.07 (38.26 to 55.56)			
Week 78 (n =252)|	51.69 (43.88 to 61.58)			
Week 90 (n = 222)|	57.33 (47.37 to 67.01)			
Week 102 (n = 191)|	59.69 (52.13 to 70.94)			

Statistical analyses

No statistical analyses for this end point

Secondary: Long Term Evaluation: Seizure free rates by time window

End point title	Long Term Evaluation: Seizure free rates by time window

End point description:

End point type	Secondary

End point timeframe:

Baseline (8-week period before start of everolimus), Week 7 to 18, Week 19 to 30, and 12 weeks thereafter until end of extension phase

End point values	Everolimus Long Term Evaluation			
Subject group type	Subject analysis set			
Number of subjects analysed	361			
Units: Percentage of seizure-free events				
number (confidence interval 95%)				
Week 18 (n = 352)|	3.98 (2.2 to 6.6)			
Week 30 (n = 335)|	6.87 (4.4 to 10.1)			
Week 42 (n = 320)|	8.44 (5.6 to 12.0)			
Week 54 (n = 299)|	8.70 (5.8 to 12.5)			

Week 66 (n = 282)|	10.99 (7.6 to 15.2)			
Week 78 (n = 252)|	13.49 (9.5 to 18.3)			
Week 90 (n = 222)|	14.86 (10.5 to 20.2)			
Week 102 (n = 191)|	15.18 (10.4 to 21.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Core Phase: Incidence of suicide attempt, suicidal ideation or behavior during Core phase per Columbia Suicide Severity Rating Scale (C-SSRS) outcomes

End point title	Core Phase: Incidence of suicide attempt, suicidal ideation or behavior during Core phase per Columbia Suicide Severity Rating Scale (C-SSRS) outcomes

End point description:

Comparison of suicidality using the C-SSRS in the everolimus low-trough treatment arm (3-7 ng/mL), high-trough treatment arm (9-15 ng/mL) and placebo arm. The Columbia-Suicide Severity Rating Scale (C-SSRS) is a questionnaire used for suicide assessment developed by multiple institutions, including Columbia University, with NIMH support. The scale is evidence-supported and is part of a national and international public health initiative involving the assessment of suicidality. There are different scoring systems depending on the population. The important elements to note are that the higher the scores on the individual items and the more "yes" items, the higher the suicide risk.

End point type	Secondary

End point timeframe:

Baseline, Week 18

End point values	Everolimus LT target of 3 to 7 ng/mL	Everolimus HT target of 9 to 15 ng/mL	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	117	130	119	
Units: Participants				
Completed suicide|	0	0	0	
Suicide attempt|	1	0	0	
Prep actions toward imminent suicidal behavior|	2	0	0	
Suicidal ideation|	3	1	0	
Self-injurious behavior without suicide intent|	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Long Term Evaluation: Incidence of suicide attempt, suicidal ideation or

behavior during Core phase per Columbia Suicide Severity Rating Scale (C-SSRS) outcomes

End point title	Long Term Evaluation: Incidence of suicide attempt, suicidal ideation or behavior during Core phase per Columbia Suicide Severity Rating Scale (C-SSRS) outcomes

End point description:

Suicidality using the C-SSRS for all everolimus treated patients. The Columbia-Suicide Severity Rating Scale (C-SSRS) is a questionnaire used for suicide assessment developed by multiple institutions, including Columbia University, with NIMH support. The scale is evidence-supported and is part of a national and international public health initiative involving the assessment of suicidality. There are different scoring systems depending on the population. The important elements to note are that the higher the scores on the individual items and the more "yes" items, the higher the suicide risk.

End point type	Secondary

End point timeframe:

During everolimus treatment from start of everolimus to end of everolimus

End point values	Everolimus Long Term Evaluation			
Subject group type	Subject analysis set			
Number of subjects analysed	361			
Units: Participants				
Completed suicide|	0			
Suicidal attempt|	1			
Prep. actions toward imminent suicidal behavior|	2			
Suicidal ideation|	7			
Self-injurious behavior without suicide intent|	1			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from start of everolimus until LPLV. AEs while on placebo period were not counted in the tables below.

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	20.1

Reporting groups

Reporting group title	Everolimus 3-7 ng/ml

Reporting group description:

Participants received everolimus dispersible tablets for oral suspension with titration to a low trough (LT) range of 3 to 7 ng/mL

Reporting group title	Everolimus start Ext

Reporting group description:

Participants received everolimus dispersible tablets for oral suspension

Reporting group title	Everolimus 9-15 ng/ml

Reporting group description:

Participants received everolimus dispersible tablets for oral suspension with titration to a high trough (HT) range of 9 to 15 ng/mL

Reporting group title	Everolimus All

Reporting group description:

Participants received everolimus dispersible tablets for oral suspension in Core, Extension or Post-Extension Phase

Serious adverse events	Everolimus 3-7 ng/ml	Everolimus start Ext	Everolimus 9-15 ng/ml
Total subjects affected by serious adverse events			
subjects affected / exposed	50 / 117 (42.74%)	38 / 114 (33.33%)	49 / 130 (37.69%)
number of deaths (all causes)	1	1	2
number of deaths resulting from adverse events	1	1	0
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 117 (0.85%)	0 / 114 (0.00%)	0 / 130 (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			

Asthenia			
subjects affected / exposed	1 / 117 (0.85%)	0 / 114 (0.00%)	0 / 130 (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
Fatigue			
subjects affected / exposed	0 / 117 (0.00%)	0 / 114 (0.00%)	2 / 130 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	5 / 117 (4.27%)	2 / 114 (1.75%)	4 / 130 (3.08%)
occurrences causally related to treatment / all	5 / 7	2 / 2	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden unexplained death in epilepsy			
subjects affected / exposed	0 / 117 (0.00%)	0 / 114 (0.00%)	2 / 130 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 117 (0.85%)	0 / 114 (0.00%)	0 / 130 (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
Social circumstances			
Sexual abuse			
subjects affected / exposed	0 / 117 (0.00%)	1 / 114 (0.88%)	0 / 130 (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
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	1 / 117 (0.85%)	0 / 114 (0.00%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Aspiration			

subjects affected / exposed	1 / 117 (0.85%)	0 / 114 (0.00%)	0 / 130 (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
Cough			
subjects affected / exposed	1 / 117 (0.85%)	1 / 114 (0.88%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	0 / 117 (0.00%)	0 / 114 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung disorder			
subjects affected / exposed	0 / 117 (0.00%)	0 / 114 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	1 / 117 (0.85%)	0 / 114 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 117 (0.00%)	1 / 114 (0.88%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary haemorrhage			
subjects affected / exposed	0 / 117 (0.00%)	0 / 114 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 117 (0.85%)	0 / 114 (0.00%)	1 / 130 (0.77%)
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 disorders			
Affect lability			

subjects affected / exposed	0 / 117 (0.00%)	1 / 114 (0.88%)	0 / 130 (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
Aggression			
subjects affected / exposed	1 / 117 (0.85%)	0 / 114 (0.00%)	0 / 130 (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
Confusional state			
subjects affected / exposed	0 / 117 (0.00%)	0 / 114 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Insomnia			
subjects affected / exposed	1 / 117 (0.85%)	0 / 114 (0.00%)	0 / 130 (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
Mental status changes			
subjects affected / exposed	0 / 117 (0.00%)	0 / 114 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mood altered			
subjects affected / exposed	1 / 117 (0.85%)	0 / 114 (0.00%)	0 / 130 (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
Psychotic disorder			
subjects affected / exposed	0 / 117 (0.00%)	0 / 114 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 117 (0.00%)	0 / 114 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oxygen saturation decreased			

subjects affected / exposed	1 / 117 (0.85%)	0 / 114 (0.00%)	0 / 130 (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
Urine output decreased			
subjects affected / exposed	1 / 117 (0.85%)	0 / 114 (0.00%)	0 / 130 (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
Injury, poisoning and procedural complications			
Craniocerebral injury			
subjects affected / exposed	1 / 117 (0.85%)	0 / 114 (0.00%)	0 / 130 (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
Fall			
subjects affected / exposed	2 / 117 (1.71%)	0 / 114 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	1 / 117 (0.85%)	0 / 114 (0.00%)	0 / 130 (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
Head injury			
subjects affected / exposed	1 / 117 (0.85%)	0 / 114 (0.00%)	0 / 130 (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
Humerus fracture			
subjects affected / exposed	0 / 117 (0.00%)	0 / 114 (0.00%)	2 / 130 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	1 / 117 (0.85%)	0 / 114 (0.00%)	0 / 130 (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
Tongue injury			

subjects affected / exposed	1 / 117 (0.85%)	0 / 114 (0.00%)	0 / 130 (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	0 / 117 (0.00%)	0 / 114 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 117 (0.00%)	0 / 114 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Ataxia			
subjects affected / exposed	1 / 117 (0.85%)	2 / 114 (1.75%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 117 (0.00%)	0 / 114 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyskinesia			
subjects affected / exposed	1 / 117 (0.85%)	0 / 114 (0.00%)	0 / 130 (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
Encephalopathy			
subjects affected / exposed	1 / 117 (0.85%)	0 / 114 (0.00%)	0 / 130 (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 / 117 (1.71%)	0 / 114 (0.00%)	0 / 130 (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
Febrile convulsion			

subjects affected / exposed	1 / 117 (0.85%)	0 / 114 (0.00%)	0 / 130 (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
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 117 (0.00%)	1 / 114 (0.88%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 117 (0.00%)	0 / 114 (0.00%)	2 / 130 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	1 / 117 (0.85%)	0 / 114 (0.00%)	0 / 130 (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
Lethargy			
subjects affected / exposed	1 / 117 (0.85%)	0 / 114 (0.00%)	0 / 130 (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
Loss of consciousness			
subjects affected / exposed	0 / 117 (0.00%)	1 / 114 (0.88%)	0 / 130 (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
Moyamoya disease			
subjects affected / exposed	0 / 117 (0.00%)	0 / 114 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	7 / 117 (5.98%)	4 / 114 (3.51%)	7 / 130 (5.38%)
occurrences causally related to treatment / all	2 / 9	0 / 5	2 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure cluster			

subjects affected / exposed	1 / 117 (0.85%)	0 / 114 (0.00%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Status epilepticus			
subjects affected / exposed	7 / 117 (5.98%)	2 / 114 (1.75%)	6 / 130 (4.62%)
occurrences causally related to treatment / all	2 / 9	2 / 2	2 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stupor			
subjects affected / exposed	1 / 117 (0.85%)	0 / 114 (0.00%)	0 / 130 (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
Tremor			
subjects affected / exposed	1 / 117 (0.85%)	0 / 114 (0.00%)	0 / 130 (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			
Anaemia			
subjects affected / exposed	2 / 117 (1.71%)	1 / 114 (0.88%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	1 / 117 (0.85%)	0 / 114 (0.00%)	0 / 130 (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
Leukocytosis			
subjects affected / exposed	0 / 117 (0.00%)	0 / 114 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	1 / 117 (0.85%)	0 / 114 (0.00%)	0 / 130 (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
Pancytopenia			

subjects affected / exposed	1 / 117 (0.85%)	0 / 114 (0.00%)	0 / 130 (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
Thrombocytopenia			
subjects affected / exposed	1 / 117 (0.85%)	1 / 114 (0.88%)	0 / 130 (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
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 117 (0.85%)	0 / 114 (0.00%)	0 / 130 (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
Eye disorders			
Blepharitis			
subjects affected / exposed	1 / 117 (0.85%)	0 / 114 (0.00%)	0 / 130 (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
Meibomianitis			
subjects affected / exposed	1 / 117 (0.85%)	0 / 114 (0.00%)	0 / 130 (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
Retinal detachment			
subjects affected / exposed	0 / 117 (0.00%)	1 / 114 (0.88%)	0 / 130 (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
Retinopathy proliferative			
subjects affected / exposed	0 / 117 (0.00%)	1 / 114 (0.88%)	0 / 130 (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 disorders			
Abdominal distension			
subjects affected / exposed	0 / 117 (0.00%)	0 / 114 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Abdominal pain			
subjects affected / exposed	0 / 117 (0.00%)	1 / 114 (0.88%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 117 (0.00%)	0 / 114 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	3 / 117 (2.56%)	0 / 114 (0.00%)	2 / 130 (1.54%)
occurrences causally related to treatment / all	2 / 3	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Food poisoning			
subjects affected / exposed	1 / 117 (0.85%)	0 / 114 (0.00%)	0 / 130 (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 ileus			
subjects affected / exposed	0 / 117 (0.00%)	0 / 114 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 117 (0.85%)	0 / 114 (0.00%)	0 / 130 (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
Intestinal ischaemia			
subjects affected / exposed	0 / 117 (0.00%)	0 / 114 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mouth ulceration			
subjects affected / exposed	3 / 117 (2.56%)	1 / 114 (0.88%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			

subjects affected / exposed	0 / 117 (0.00%)	0 / 114 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	2 / 117 (1.71%)	1 / 114 (0.88%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	2 / 2	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Swollen tongue			
subjects affected / exposed	1 / 117 (0.85%)	0 / 114 (0.00%)	0 / 130 (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 / 117 (0.85%)	2 / 114 (1.75%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	1 / 117 (0.85%)	0 / 114 (0.00%)	0 / 130 (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
Skin and subcutaneous tissue disorders			
Erythema nodosum			
subjects affected / exposed	0 / 117 (0.00%)	1 / 114 (0.88%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			
subjects affected / exposed	0 / 117 (0.00%)	0 / 114 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash generalised			
subjects affected / exposed	0 / 117 (0.00%)	1 / 114 (0.88%)	0 / 130 (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
Skin lesion			

subjects affected / exposed	1 / 117 (0.85%)	0 / 114 (0.00%)	0 / 130 (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			
Acute kidney injury			
subjects affected / exposed	1 / 117 (0.85%)	0 / 114 (0.00%)	0 / 130 (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
Post streptococcal glomerulonephritis			
subjects affected / exposed	1 / 117 (0.85%)	0 / 114 (0.00%)	0 / 130 (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			
Arthralgia			
subjects affected / exposed	1 / 117 (0.85%)	0 / 114 (0.00%)	0 / 130 (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	0 / 117 (0.00%)	1 / 114 (0.88%)	0 / 130 (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
Abscess limb			
subjects affected / exposed	0 / 117 (0.00%)	1 / 114 (0.88%)	0 / 130 (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
Appendicitis			
subjects affected / exposed	0 / 117 (0.00%)	0 / 114 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	0 / 117 (0.00%)	0 / 114 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Bronchitis			
subjects affected / exposed	1 / 117 (0.85%)	2 / 114 (1.75%)	3 / 130 (2.31%)
occurrences causally related to treatment / all	0 / 1	1 / 2	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Campylobacter colitis			
subjects affected / exposed	0 / 117 (0.00%)	1 / 114 (0.88%)	0 / 130 (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
Cellulitis			
subjects affected / exposed	1 / 117 (0.85%)	2 / 114 (1.75%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	1 / 1	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Corona virus infection			
subjects affected / exposed	0 / 117 (0.00%)	0 / 114 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Croup infectious			
subjects affected / exposed	1 / 117 (0.85%)	0 / 114 (0.00%)	2 / 130 (1.54%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dacryocanaliculitis			
subjects affected / exposed	1 / 117 (0.85%)	0 / 114 (0.00%)	0 / 130 (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			
subjects affected / exposed	1 / 117 (0.85%)	1 / 114 (0.88%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile infection			
subjects affected / exposed	0 / 117 (0.00%)	1 / 114 (0.88%)	0 / 130 (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
Gastroenteritis			

subjects affected / exposed	5 / 117 (4.27%)	4 / 114 (3.51%)	5 / 130 (3.85%)
occurrences causally related to treatment / all	3 / 6	2 / 5	2 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 117 (0.00%)	1 / 114 (0.88%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal infection			
subjects affected / exposed	0 / 117 (0.00%)	0 / 114 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
H1N1 influenza			
subjects affected / exposed	0 / 117 (0.00%)	1 / 114 (0.88%)	0 / 130 (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
Herpangina			
subjects affected / exposed	1 / 117 (0.85%)	0 / 114 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	3 / 117 (2.56%)	2 / 114 (1.75%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	1 / 3	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	1 / 117 (0.85%)	1 / 114 (0.88%)	0 / 130 (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
Lung infection			
subjects affected / exposed	1 / 117 (0.85%)	0 / 114 (0.00%)	0 / 130 (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
Mastoiditis			

subjects affected / exposed	0 / 117 (0.00%)	1 / 114 (0.88%)	0 / 130 (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
Meningitis			
subjects affected / exposed	0 / 117 (0.00%)	1 / 114 (0.88%)	0 / 130 (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
Oral herpes			
subjects affected / exposed	1 / 117 (0.85%)	0 / 114 (0.00%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	0 / 117 (0.00%)	0 / 114 (0.00%)	2 / 130 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media			
subjects affected / exposed	0 / 117 (0.00%)	1 / 114 (0.88%)	0 / 130 (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
Periorbital cellulitis			
subjects affected / exposed	0 / 117 (0.00%)	0 / 114 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Perirectal abscess			
subjects affected / exposed	1 / 117 (0.85%)	0 / 114 (0.00%)	0 / 130 (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
Pharyngitis			
subjects affected / exposed	2 / 117 (1.71%)	1 / 114 (0.88%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngitis streptococcal			

subjects affected / exposed	0 / 117 (0.00%)	0 / 114 (0.00%)	2 / 130 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	16 / 117 (13.68%)	9 / 114 (7.89%)	13 / 130 (10.00%)
occurrences causally related to treatment / all	9 / 18	10 / 13	9 / 16
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 117 (0.00%)	1 / 114 (0.88%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia influenzal			
subjects affected / exposed	1 / 117 (0.85%)	0 / 114 (0.00%)	0 / 130 (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
Pneumonia mycoplasmal			
subjects affected / exposed	2 / 117 (1.71%)	1 / 114 (0.88%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia viral			
subjects affected / exposed	0 / 117 (0.00%)	2 / 114 (1.75%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudocroup			
subjects affected / exposed	1 / 117 (0.85%)	0 / 114 (0.00%)	0 / 130 (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
Pyelonephritis			
subjects affected / exposed	2 / 117 (1.71%)	0 / 114 (0.00%)	2 / 130 (1.54%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			

subjects affected / exposed	0 / 117 (0.00%)	1 / 114 (0.88%)	0 / 130 (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
Respiratory tract infection			
subjects affected / exposed	0 / 117 (0.00%)	1 / 114 (0.88%)	0 / 130 (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
Rotavirus infection			
subjects affected / exposed	0 / 117 (0.00%)	0 / 114 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 117 (0.85%)	0 / 114 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 117 (0.00%)	1 / 114 (0.88%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Sinusitis			
subjects affected / exposed	1 / 117 (0.85%)	1 / 114 (0.88%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin infection			
subjects affected / exposed	0 / 117 (0.00%)	1 / 114 (0.88%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	0 / 117 (0.00%)	3 / 114 (2.63%)	2 / 130 (1.54%)
occurrences causally related to treatment / all	0 / 0	1 / 3	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth abscess			

subjects affected / exposed	0 / 117 (0.00%)	1 / 114 (0.88%)	0 / 130 (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
Tooth infection			
subjects affected / exposed	1 / 117 (0.85%)	0 / 114 (0.00%)	0 / 130 (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
Upper respiratory tract infection			
subjects affected / exposed	1 / 117 (0.85%)	0 / 114 (0.00%)	0 / 130 (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
Urinary tract infection			
subjects affected / exposed	3 / 117 (2.56%)	0 / 114 (0.00%)	0 / 130 (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
Urosepsis			
subjects affected / exposed	0 / 117 (0.00%)	1 / 114 (0.88%)	0 / 130 (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
Varicella			
subjects affected / exposed	1 / 117 (0.85%)	1 / 114 (0.88%)	0 / 130 (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
Viraemia			
subjects affected / exposed	0 / 117 (0.00%)	1 / 114 (0.88%)	0 / 130 (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
Viral infection			
subjects affected / exposed	0 / 117 (0.00%)	3 / 114 (2.63%)	0 / 130 (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
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	2 / 117 (1.71%)	0 / 114 (0.00%)	0 / 130 (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
Dehydration			
subjects affected / exposed	1 / 117 (0.85%)	1 / 114 (0.88%)	0 / 130 (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
Feeding intolerance			
subjects affected / exposed	1 / 117 (0.85%)	0 / 114 (0.00%)	0 / 130 (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
Hypocalcaemia			
subjects affected / exposed	0 / 117 (0.00%)	0 / 114 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 117 (0.00%)	0 / 114 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	1 / 117 (0.85%)	0 / 114 (0.00%)	0 / 130 (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
Hypophagia			
subjects affected / exposed	1 / 117 (0.85%)	0 / 114 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophosphataemia			
subjects affected / exposed	0 / 117 (0.00%)	0 / 114 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Everolimus All		
Total subjects affected by serious			

adverse events			
subjects affected / exposed	137 / 361 (37.95%)		
number of deaths (all causes)	4		
number of deaths resulting from adverse events	2		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 361 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 361 (0.28%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Fatigue			
subjects affected / exposed	2 / 361 (0.55%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	11 / 361 (3.05%)		
occurrences causally related to treatment / all	10 / 13		
deaths causally related to treatment / all	0 / 0		
Sudden unexplained death in epilepsy			
subjects affected / exposed	2 / 361 (0.55%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 361 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Social circumstances			
Sexual abuse			

subjects affected / exposed	1 / 361 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	1 / 361 (0.28%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	1 / 361 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cough			
subjects affected / exposed	2 / 361 (0.55%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Interstitial lung disease			
subjects affected / exposed	1 / 361 (0.28%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lung disorder			
subjects affected / exposed	1 / 361 (0.28%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia aspiration			
subjects affected / exposed	2 / 361 (0.55%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Pneumonitis			
subjects affected / exposed	2 / 361 (0.55%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Pulmonary haemorrhage				
subjects affected / exposed	1 / 361 (0.28%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	2 / 361 (0.55%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Affect lability				
subjects affected / exposed	1 / 361 (0.28%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Aggression				
subjects affected / exposed	1 / 361 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Confusional state				
subjects affected / exposed	1 / 361 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Insomnia				
subjects affected / exposed	1 / 361 (0.28%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Mental status changes				
subjects affected / exposed	1 / 361 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Mood altered				
subjects affected / exposed	1 / 361 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychotic disorder				

subjects affected / exposed	1 / 361 (0.28%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	1 / 361 (0.28%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Oxygen saturation decreased			
subjects affected / exposed	1 / 361 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urine output decreased			
subjects affected / exposed	1 / 361 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Craniocerebral injury			
subjects affected / exposed	1 / 361 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	3 / 361 (0.83%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Femur fracture			
subjects affected / exposed	1 / 361 (0.28%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Head injury			
subjects affected / exposed	1 / 361 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Humerus fracture				
subjects affected / exposed	2 / 361 (0.55%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Tibia fracture				
subjects affected / exposed	1 / 361 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tongue injury				
subjects affected / exposed	1 / 361 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Toxicity to various agents				
subjects affected / exposed	1 / 361 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Cardiac arrest				
subjects affected / exposed	1 / 361 (0.28%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Ataxia				
subjects affected / exposed	3 / 361 (0.83%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Dizziness				
subjects affected / exposed	1 / 361 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyskinesia				
subjects affected / exposed	1 / 361 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Encephalopathy			
subjects affected / exposed	1 / 361 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Epilepsy			
subjects affected / exposed	2 / 361 (0.55%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Febrile convulsion			
subjects affected / exposed	1 / 361 (0.28%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Generalised tonic-clonic seizure			
subjects affected / exposed	2 / 361 (0.55%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	2 / 361 (0.55%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Ischaemic stroke			
subjects affected / exposed	1 / 361 (0.28%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lethargy			
subjects affected / exposed	1 / 361 (0.28%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Loss of consciousness			
subjects affected / exposed	1 / 361 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Moyamoya disease			

subjects affected / exposed	1 / 361 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Seizure				
subjects affected / exposed	18 / 361 (4.99%)			
occurrences causally related to treatment / all	4 / 22			
deaths causally related to treatment / all	0 / 0			
Seizure cluster				
subjects affected / exposed	1 / 361 (0.28%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Status epilepticus				
subjects affected / exposed	15 / 361 (4.16%)			
occurrences causally related to treatment / all	6 / 17			
deaths causally related to treatment / all	0 / 0			
Stupor				
subjects affected / exposed	1 / 361 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tremor				
subjects affected / exposed	1 / 361 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	3 / 361 (0.83%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				
subjects affected / exposed	1 / 361 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Leukocytosis				

subjects affected / exposed	1 / 361 (0.28%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Leukopenia				
subjects affected / exposed	1 / 361 (0.28%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pancytopenia				
subjects affected / exposed	1 / 361 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
subjects affected / exposed	2 / 361 (0.55%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Ear and labyrinth disorders				
Ear pain				
subjects affected / exposed	1 / 361 (0.28%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Eye disorders				
Blepharitis				
subjects affected / exposed	1 / 361 (0.28%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Meibomianitis				
subjects affected / exposed	1 / 361 (0.28%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Retinal detachment				
subjects affected / exposed	1 / 361 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Retinopathy proliferative				

subjects affected / exposed	1 / 361 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 361 (0.28%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	2 / 361 (0.55%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	1 / 361 (0.28%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	5 / 361 (1.39%)		
occurrences causally related to treatment / all	3 / 6		
deaths causally related to treatment / all	0 / 0		
Food poisoning			
subjects affected / exposed	1 / 361 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric ileus			
subjects affected / exposed	1 / 361 (0.28%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 361 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal ischaemia			

subjects affected / exposed	1 / 361 (0.28%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Mouth ulceration				
subjects affected / exposed	4 / 361 (1.11%)			
occurrences causally related to treatment / all	3 / 4			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	1 / 361 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Stomatitis				
subjects affected / exposed	4 / 361 (1.11%)			
occurrences causally related to treatment / all	3 / 4			
deaths causally related to treatment / all	0 / 0			
Swollen tongue				
subjects affected / exposed	1 / 361 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	4 / 361 (1.11%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Hepatitis				
subjects affected / exposed	1 / 361 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Erythema nodosum				
subjects affected / exposed	2 / 361 (0.55%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Rash				

subjects affected / exposed	1 / 361 (0.28%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Rash generalised			
subjects affected / exposed	1 / 361 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin lesion			
subjects affected / exposed	1 / 361 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 361 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post streptococcal glomerulonephritis			
subjects affected / exposed	1 / 361 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 361 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abscess			
subjects affected / exposed	1 / 361 (0.28%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Abscess limb			
subjects affected / exposed	1 / 361 (0.28%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Appendicitis			
subjects affected / exposed	1 / 361 (0.28%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Bacteraemia			
subjects affected / exposed	1 / 361 (0.28%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	6 / 361 (1.66%)		
occurrences causally related to treatment / all	3 / 6		
deaths causally related to treatment / all	0 / 0		
Campylobacter colitis			
subjects affected / exposed	1 / 361 (0.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	3 / 361 (0.83%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Corona virus infection			
subjects affected / exposed	1 / 361 (0.28%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Croup infectious			
subjects affected / exposed	3 / 361 (0.83%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Dacryocanaliculitis			
subjects affected / exposed	1 / 361 (0.28%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ear infection			

subjects affected / exposed	2 / 361 (0.55%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Febrile infection				
subjects affected / exposed	1 / 361 (0.28%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	14 / 361 (3.88%)			
occurrences causally related to treatment / all	7 / 16			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis viral				
subjects affected / exposed	2 / 361 (0.55%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal infection				
subjects affected / exposed	1 / 361 (0.28%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
H1N1 influenza				
subjects affected / exposed	1 / 361 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Herpangina				
subjects affected / exposed	2 / 361 (0.55%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	6 / 361 (1.66%)			
occurrences causally related to treatment / all	1 / 6			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				

subjects affected / exposed	2 / 361 (0.55%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Lung infection				
subjects affected / exposed	1 / 361 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Mastoiditis				
subjects affected / exposed	1 / 361 (0.28%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Meningitis				
subjects affected / exposed	1 / 361 (0.28%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Oral herpes				
subjects affected / exposed	1 / 361 (0.28%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Osteomyelitis				
subjects affected / exposed	2 / 361 (0.55%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Otitis media				
subjects affected / exposed	1 / 361 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Periorbital cellulitis				
subjects affected / exposed	1 / 361 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Perirectal abscess				

subjects affected / exposed	1 / 361 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pharyngitis				
subjects affected / exposed	4 / 361 (1.11%)			
occurrences causally related to treatment / all	3 / 4			
deaths causally related to treatment / all	0 / 0			
Pharyngitis streptococcal				
subjects affected / exposed	2 / 361 (0.55%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	38 / 361 (10.53%)			
occurrences causally related to treatment / all	28 / 47			
deaths causally related to treatment / all	1 / 1			
Pneumonia bacterial				
subjects affected / exposed	2 / 361 (0.55%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Pneumonia influenzal				
subjects affected / exposed	1 / 361 (0.28%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia mycoplasmal				
subjects affected / exposed	3 / 361 (0.83%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Pneumonia viral				
subjects affected / exposed	3 / 361 (0.83%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Pseudocroup				

subjects affected / exposed	1 / 361 (0.28%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				
subjects affected / exposed	4 / 361 (1.11%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis acute				
subjects affected / exposed	1 / 361 (0.28%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				
subjects affected / exposed	1 / 361 (0.28%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Rotavirus infection				
subjects affected / exposed	1 / 361 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	2 / 361 (0.55%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	2 / 361 (0.55%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	1 / 1			
Sinusitis				
subjects affected / exposed	3 / 361 (0.83%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Skin infection				

subjects affected / exposed	2 / 361 (0.55%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Tonsillitis				
subjects affected / exposed	5 / 361 (1.39%)			
occurrences causally related to treatment / all	2 / 5			
deaths causally related to treatment / all	0 / 0			
Tooth abscess				
subjects affected / exposed	1 / 361 (0.28%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Tooth infection				
subjects affected / exposed	1 / 361 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				
subjects affected / exposed	1 / 361 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	3 / 361 (0.83%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	1 / 361 (0.28%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Varicella				
subjects affected / exposed	2 / 361 (0.55%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Viraemia				

subjects affected / exposed	1 / 361 (0.28%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Viral infection				
subjects affected / exposed	3 / 361 (0.83%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Decreased appetite				
subjects affected / exposed	2 / 361 (0.55%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Dehydration				
subjects affected / exposed	2 / 361 (0.55%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Feeding intolerance				
subjects affected / exposed	1 / 361 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypocalcaemia				
subjects affected / exposed	1 / 361 (0.28%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypokalaemia				
subjects affected / exposed	1 / 361 (0.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hyponatraemia				
subjects affected / exposed	1 / 361 (0.28%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hypophagia				

subjects affected / exposed	2 / 361 (0.55%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Hypophosphataemia			
subjects affected / exposed	1 / 361 (0.28%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Everolimus 3-7 ng/ml	Everolimus start Ext	Everolimus 9-15 ng/ml
Total subjects affected by non-serious adverse events			
subjects affected / exposed	110 / 117 (94.02%)	109 / 114 (95.61%)	126 / 130 (96.92%)
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 117 (5.13%)	6 / 114 (5.26%)	7 / 130 (5.38%)
occurrences (all)	7	6	9
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	8 / 117 (6.84%)	5 / 114 (4.39%)	11 / 130 (8.46%)
occurrences (all)	9	6	16
Pyrexia			
subjects affected / exposed	47 / 117 (40.17%)	31 / 114 (27.19%)	56 / 130 (43.08%)
occurrences (all)	120	70	127
Reproductive system and breast disorders			
Menstruation irregular			
subjects affected / exposed	1 / 117 (0.85%)	3 / 114 (2.63%)	7 / 130 (5.38%)
occurrences (all)	2	5	14
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	29 / 117 (24.79%)	15 / 114 (13.16%)	33 / 130 (25.38%)
occurrences (all)	57	25	64
Epistaxis			

subjects affected / exposed	4 / 117 (3.42%)	3 / 114 (2.63%)	12 / 130 (9.23%)
occurrences (all)	6	3	29
Nasal congestion			
subjects affected / exposed	4 / 117 (3.42%)	1 / 114 (0.88%)	7 / 130 (5.38%)
occurrences (all)	4	1	8
Oropharyngeal pain			
subjects affected / exposed	5 / 117 (4.27%)	5 / 114 (4.39%)	10 / 130 (7.69%)
occurrences (all)	8	5	12
Rhinorrhoea			
subjects affected / exposed	10 / 117 (8.55%)	3 / 114 (2.63%)	9 / 130 (6.92%)
occurrences (all)	20	4	11
Psychiatric disorders			
Aggression			
subjects affected / exposed	5 / 117 (4.27%)	1 / 114 (0.88%)	8 / 130 (6.15%)
occurrences (all)	5	3	8
Agitation			
subjects affected / exposed	7 / 117 (5.98%)	2 / 114 (1.75%)	1 / 130 (0.77%)
occurrences (all)	8	2	1
Insomnia			
subjects affected / exposed	8 / 117 (6.84%)	2 / 114 (1.75%)	8 / 130 (6.15%)
occurrences (all)	11	2	9
Irritability			
subjects affected / exposed	5 / 117 (4.27%)	7 / 114 (6.14%)	4 / 130 (3.08%)
occurrences (all)	6	7	4
Investigations			
Blood cholesterol increased			
subjects affected / exposed	14 / 117 (11.97%)	17 / 114 (14.91%)	20 / 130 (15.38%)
occurrences (all)	20	19	30
Blood triglycerides increased			
subjects affected / exposed	5 / 117 (4.27%)	6 / 114 (5.26%)	10 / 130 (7.69%)
occurrences (all)	6	7	16
Low density lipoprotein increased			
subjects affected / exposed	6 / 117 (5.13%)	3 / 114 (2.63%)	8 / 130 (6.15%)
occurrences (all)	8	4	13
Weight decreased			

subjects affected / exposed	10 / 117 (8.55%)	8 / 114 (7.02%)	7 / 130 (5.38%)
occurrences (all)	11	9	9
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	2 / 117 (1.71%)	1 / 114 (0.88%)	7 / 130 (5.38%)
occurrences (all)	3	1	10
Contusion			
subjects affected / exposed	5 / 117 (4.27%)	3 / 114 (2.63%)	8 / 130 (6.15%)
occurrences (all)	6	4	8
Fall			
subjects affected / exposed	15 / 117 (12.82%)	8 / 114 (7.02%)	10 / 130 (7.69%)
occurrences (all)	21	9	17
Laceration			
subjects affected / exposed	3 / 117 (2.56%)	6 / 114 (5.26%)	4 / 130 (3.08%)
occurrences (all)	3	11	4
Skin abrasion			
subjects affected / exposed	6 / 117 (5.13%)	2 / 114 (1.75%)	5 / 130 (3.85%)
occurrences (all)	6	2	9
Nervous system disorders			
Headache			
subjects affected / exposed	19 / 117 (16.24%)	10 / 114 (8.77%)	19 / 130 (14.62%)
occurrences (all)	34	60	28
Somnolence			
subjects affected / exposed	8 / 117 (6.84%)	4 / 114 (3.51%)	9 / 130 (6.92%)
occurrences (all)	12	5	9
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	10 / 117 (8.55%)	4 / 114 (3.51%)	7 / 130 (5.38%)
occurrences (all)	13	4	11
Neutropenia			
subjects affected / exposed	4 / 117 (3.42%)	1 / 114 (0.88%)	9 / 130 (6.92%)
occurrences (all)	5	1	14
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	10 / 117 (8.55%)	5 / 114 (4.39%)	4 / 130 (3.08%)
occurrences (all)	13	6	7

Abdominal pain upper			
subjects affected / exposed	7 / 117 (5.98%)	5 / 114 (4.39%)	10 / 130 (7.69%)
occurrences (all)	8	5	14
Aphthous ulcer			
subjects affected / exposed	11 / 117 (9.40%)	10 / 114 (8.77%)	23 / 130 (17.69%)
occurrences (all)	21	17	56
Constipation			
subjects affected / exposed	9 / 117 (7.69%)	7 / 114 (6.14%)	12 / 130 (9.23%)
occurrences (all)	9	7	12
Dental caries			
subjects affected / exposed	6 / 117 (5.13%)	3 / 114 (2.63%)	2 / 130 (1.54%)
occurrences (all)	10	3	2
Diarrhoea			
subjects affected / exposed	45 / 117 (38.46%)	30 / 114 (26.32%)	42 / 130 (32.31%)
occurrences (all)	97	57	83
Mouth ulceration			
subjects affected / exposed	36 / 117 (30.77%)	22 / 114 (19.30%)	44 / 130 (33.85%)
occurrences (all)	157	77	130
Nausea			
subjects affected / exposed	6 / 117 (5.13%)	3 / 114 (2.63%)	7 / 130 (5.38%)
occurrences (all)	8	3	9
Stomatitis			
subjects affected / exposed	41 / 117 (35.04%)	41 / 114 (35.96%)	48 / 130 (36.92%)
occurrences (all)	84	120	110
Vomiting			
subjects affected / exposed	28 / 117 (23.93%)	16 / 114 (14.04%)	35 / 130 (26.92%)
occurrences (all)	109	36	47
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	6 / 117 (5.13%)	6 / 114 (5.26%)	14 / 130 (10.77%)
occurrences (all)	6	7	17
Alopecia			
subjects affected / exposed	4 / 117 (3.42%)	2 / 114 (1.75%)	8 / 130 (6.15%)
occurrences (all)	4	2	10
Dermatitis			

subjects affected / exposed	7 / 117 (5.98%)	2 / 114 (1.75%)	2 / 130 (1.54%)
occurrences (all)	7	2	2
Dry skin			
subjects affected / exposed	6 / 117 (5.13%)	2 / 114 (1.75%)	3 / 130 (2.31%)
occurrences (all)	7	2	3
Rash			
subjects affected / exposed	14 / 117 (11.97%)	13 / 114 (11.40%)	21 / 130 (16.15%)
occurrences (all)	22	16	30
Infections and infestations			
Bronchitis			
subjects affected / exposed	11 / 117 (9.40%)	8 / 114 (7.02%)	17 / 130 (13.08%)
occurrences (all)	19	8	31
Conjunctivitis			
subjects affected / exposed	11 / 117 (9.40%)	6 / 114 (5.26%)	8 / 130 (6.15%)
occurrences (all)	21	6	8
Ear infection			
subjects affected / exposed	11 / 117 (9.40%)	3 / 114 (2.63%)	19 / 130 (14.62%)
occurrences (all)	12	4	23
Gastroenteritis			
subjects affected / exposed	13 / 117 (11.11%)	7 / 114 (6.14%)	15 / 130 (11.54%)
occurrences (all)	16	9	18
Gingivitis			
subjects affected / exposed	9 / 117 (7.69%)	0 / 114 (0.00%)	4 / 130 (3.08%)
occurrences (all)	9	0	5
Hordeolum			
subjects affected / exposed	6 / 117 (5.13%)	4 / 114 (3.51%)	5 / 130 (3.85%)
occurrences (all)	7	4	8
Influenza			
subjects affected / exposed	16 / 117 (13.68%)	9 / 114 (7.89%)	18 / 130 (13.85%)
occurrences (all)	19	14	21
Lower respiratory tract infection			
subjects affected / exposed	7 / 117 (5.98%)	2 / 114 (1.75%)	1 / 130 (0.77%)
occurrences (all)	23	4	1
Nasopharyngitis			
subjects affected / exposed	33 / 117 (28.21%)	26 / 114 (22.81%)	35 / 130 (26.92%)
occurrences (all)	72	59	109

Pharyngitis			
subjects affected / exposed	11 / 117 (9.40%)	8 / 114 (7.02%)	18 / 130 (13.85%)
occurrences (all)	38	17	21
Respiratory tract infection			
subjects affected / exposed	3 / 117 (2.56%)	6 / 114 (5.26%)	0 / 130 (0.00%)
occurrences (all)	4	7	0
Rhinitis			
subjects affected / exposed	9 / 117 (7.69%)	5 / 114 (4.39%)	9 / 130 (6.92%)
occurrences (all)	16	7	26
Sinusitis			
subjects affected / exposed	3 / 117 (2.56%)	8 / 114 (7.02%)	15 / 130 (11.54%)
occurrences (all)	4	9	18
Tonsillitis			
subjects affected / exposed	11 / 117 (9.40%)	4 / 114 (3.51%)	9 / 130 (6.92%)
occurrences (all)	17	4	12
Upper respiratory tract infection			
subjects affected / exposed	32 / 117 (27.35%)	22 / 114 (19.30%)	42 / 130 (32.31%)
occurrences (all)	88	59	88
Urinary tract infection			
subjects affected / exposed	12 / 117 (10.26%)	6 / 114 (5.26%)	10 / 130 (7.69%)
occurrences (all)	18	13	11
Viral infection			
subjects affected / exposed	9 / 117 (7.69%)	2 / 114 (1.75%)	7 / 130 (5.38%)
occurrences (all)	13	3	8
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	13 / 117 (11.11%)	6 / 114 (5.26%)	20 / 130 (15.38%)
occurrences (all)	20	7	26
Hyperlipidaemia			
subjects affected / exposed	4 / 117 (3.42%)	2 / 114 (1.75%)	9 / 130 (6.92%)
occurrences (all)	5	2	12
Hypertriglyceridaemia			
subjects affected / exposed	9 / 117 (7.69%)	6 / 114 (5.26%)	12 / 130 (9.23%)
occurrences (all)	12	7	13

Non-serious adverse events	Everolimus All		
Total subjects affected by non-serious			

adverse events subjects affected / exposed	345 / 361 (95.57%)		
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	19 / 361 (5.26%) 22		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	24 / 361 (6.65%) 31 134 / 361 (37.12%) 317		
Reproductive system and breast disorders Menstruation irregular subjects affected / exposed occurrences (all)	11 / 361 (3.05%) 21		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Nasal congestion subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Rhinorrhoea subjects affected / exposed occurrences (all)	77 / 361 (21.33%) 146 19 / 361 (5.26%) 38 12 / 361 (3.32%) 13 20 / 361 (5.54%) 25 22 / 361 (6.09%) 35		
Psychiatric disorders Aggression			

subjects affected / exposed	14 / 361 (3.88%)		
occurrences (all)	16		
Agitation			
subjects affected / exposed	10 / 361 (2.77%)		
occurrences (all)	11		
Insomnia			
subjects affected / exposed	18 / 361 (4.99%)		
occurrences (all)	22		
Irritability			
subjects affected / exposed	16 / 361 (4.43%)		
occurrences (all)	17		
Investigations			
Blood cholesterol increased			
subjects affected / exposed	51 / 361 (14.13%)		
occurrences (all)	69		
Blood triglycerides increased			
subjects affected / exposed	21 / 361 (5.82%)		
occurrences (all)	29		
Low density lipoprotein increased			
subjects affected / exposed	17 / 361 (4.71%)		
occurrences (all)	25		
Weight decreased			
subjects affected / exposed	25 / 361 (6.93%)		
occurrences (all)	29		
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	10 / 361 (2.77%)		
occurrences (all)	14		
Contusion			
subjects affected / exposed	16 / 361 (4.43%)		
occurrences (all)	18		
Fall			
subjects affected / exposed	33 / 361 (9.14%)		
occurrences (all)	47		
Laceration			

subjects affected / exposed	13 / 361 (3.60%)		
occurrences (all)	18		
Skin abrasion			
subjects affected / exposed	13 / 361 (3.60%)		
occurrences (all)	17		
Nervous system disorders			
Headache			
subjects affected / exposed	48 / 361 (13.30%)		
occurrences (all)	122		
Somnolence			
subjects affected / exposed	21 / 361 (5.82%)		
occurrences (all)	26		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	21 / 361 (5.82%)		
occurrences (all)	28		
Neutropenia			
subjects affected / exposed	14 / 361 (3.88%)		
occurrences (all)	20		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	19 / 361 (5.26%)		
occurrences (all)	26		
Abdominal pain upper			
subjects affected / exposed	22 / 361 (6.09%)		
occurrences (all)	27		
Aphthous ulcer			
subjects affected / exposed	44 / 361 (12.19%)		
occurrences (all)	94		
Constipation			
subjects affected / exposed	28 / 361 (7.76%)		
occurrences (all)	28		
Dental caries			
subjects affected / exposed	11 / 361 (3.05%)		
occurrences (all)	15		
Diarrhoea			

subjects affected / exposed	117 / 361 (32.41%)		
occurrences (all)	237		
Mouth ulceration			
subjects affected / exposed	102 / 361 (28.25%)		
occurrences (all)	364		
Nausea			
subjects affected / exposed	16 / 361 (4.43%)		
occurrences (all)	20		
Stomatitis			
subjects affected / exposed	130 / 361 (36.01%)		
occurrences (all)	314		
Vomiting			
subjects affected / exposed	79 / 361 (21.88%)		
occurrences (all)	192		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	26 / 361 (7.20%)		
occurrences (all)	30		
Alopecia			
subjects affected / exposed	14 / 361 (3.88%)		
occurrences (all)	16		
Dermatitis			
subjects affected / exposed	11 / 361 (3.05%)		
occurrences (all)	11		
Dry skin			
subjects affected / exposed	11 / 361 (3.05%)		
occurrences (all)	12		
Rash			
subjects affected / exposed	48 / 361 (13.30%)		
occurrences (all)	68		
Infections and infestations			
Bronchitis			
subjects affected / exposed	36 / 361 (9.97%)		
occurrences (all)	58		
Conjunctivitis			

subjects affected / exposed	25 / 361 (6.93%)			
occurrences (all)	35			
Ear infection				
subjects affected / exposed	33 / 361 (9.14%)			
occurrences (all)	39			
Gastroenteritis				
subjects affected / exposed	35 / 361 (9.70%)			
occurrences (all)	43			
Gingivitis				
subjects affected / exposed	13 / 361 (3.60%)			
occurrences (all)	14			
Hordeolum				
subjects affected / exposed	15 / 361 (4.16%)			
occurrences (all)	19			
Influenza				
subjects affected / exposed	43 / 361 (11.91%)			
occurrences (all)	54			
Lower respiratory tract infection				
subjects affected / exposed	10 / 361 (2.77%)			
occurrences (all)	28			
Nasopharyngitis				
subjects affected / exposed	94 / 361 (26.04%)			
occurrences (all)	240			
Pharyngitis				
subjects affected / exposed	37 / 361 (10.25%)			
occurrences (all)	76			
Respiratory tract infection				
subjects affected / exposed	9 / 361 (2.49%)			
occurrences (all)	11			
Rhinitis				
subjects affected / exposed	23 / 361 (6.37%)			
occurrences (all)	49			
Sinusitis				
subjects affected / exposed	26 / 361 (7.20%)			
occurrences (all)	31			
Tonsillitis				

subjects affected / exposed	24 / 361 (6.65%)		
occurrences (all)	33		
Upper respiratory tract infection			
subjects affected / exposed	96 / 361 (26.59%)		
occurrences (all)	235		
Urinary tract infection			
subjects affected / exposed	28 / 361 (7.76%)		
occurrences (all)	42		
Viral infection			
subjects affected / exposed	18 / 361 (4.99%)		
occurrences (all)	24		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	39 / 361 (10.80%)		
occurrences (all)	53		
Hyperlipidaemia			
subjects affected / exposed	15 / 361 (4.16%)		
occurrences (all)	19		
Hypertriglyceridaemia			
subjects affected / exposed	27 / 361 (7.48%)		
occurrences (all)	32		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 January 2013	Exclusion criterion regarding Lennox Gastaut Syndrome (LGS) was removed; Patients weighing <12 kg were not to be enrolled. Patients weighing 12-20 kg were not required to provide PK AED and it was recommended that TSC1/2 genetic mutation samples were collected at Visit 4 to reduce blood collection at Visit 2; Inclusion of patients aged 1 year; Improvement of wording regarding sensitivity analysis; Clarification regarding titration in both Core and Extension phases; Updates regarding rescue medication; Improving of wording for dosing age; Addition of clarifications on the inclusion criteria; Update of items under criteria for premature withdrawal; Replacing Appendix A with an updated sub-study summary that included the collection of HFO EEGs.
14 March 2014	Inclusion of additional 10 patients to the everolimus 9 to 15-ng/mL trough range arm; Inclusion criterion 3 updated to expand the definition of TSC seizures and include sensory seizures as the sole seizure type if confirmed to be partial onset by ictal EEG; The exclusion definition was modified to exclude patients < 2 years of age with untreated infantile spasms, to clarify the eligibility of patients with residual epileptic spasms and to enable such patients to be included in the study; Exclusion criterion 26 was added related to patients on a ketogenic diet (defined as <40 g of carbohydrate/day). Ketogenic diet, a type of anti-epilepsy therapy, may mediate its effect through mTOR inhibition. Because the potential interaction of similarly acting therapies may pose risks to patients, it was determined that treatment with a low carbohydrate ketogenic diet should be excluded; Allowing Investigator discretion to manage everolimus titrations in the Extension phase; The study required patients aged ≥ 13 years to complete the eC-SSRS themselves and for caregivers to complete the eC-SSRS on behalf of patients < 13 years or patients with cognitive impairment. The amendment required that Investigators discuss episodes of self-injury and changes in a patient's mood and/or behavior with the patient and caregiver, for all patients; The Vineland scale raw scores were to be collected in a separate database and not in the Clinical OC-RDC database; Correction of definition of Safety Population.
25 March 2016	Addition of new phase of the study (Post-extension phase): This change allowed patients remaining in the study to receive ongoing treatment with everolimus and for the study to extend the monitoring and collection of everolimus exposure, as well as safety measures during this longer study participation and drug exposure phase. This strategy was to allow closure of this study by 30-Oct-2017 (approximately 13 months after what would have been the end of the study, had the study been closed at the completion of the Extension phase), and the creation of a final CSR. To permit the completion of the Extension Phase and the generation of a CSR covering the Extension phase, as originally envisioned; To provide Investigators with independent control of patient dosing: This allows for more personalized and clinically relevant increases or decreases in dose titrations to more rapidly and effectively permit titration of the everolimus dose to a level that creates a desired Cmin.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported