



## 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)                          | EMA-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 frequency of partial-onset seizures on each of two trough ranges of everolimus (3 to 7 ng/mL and 9 to 15 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  $\geq 25\%$  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:

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### **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                                  |
| <b>Arm title</b>             | 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.

|                  |                                       |
|------------------|---------------------------------------|
| <b>Arm title</b> | 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.

|                  |         |
|------------------|---------|
| <b>Arm title</b> | 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.

| <b>Number of subjects in period 1</b> | Everolimus LT target<br>of 3 to 7 ng/mL | Everolimus HT target<br>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 <sup>[1]</sup>                        | 3 <sup>[2]</sup>                         | 0 <sup>[3]</sup> |
| Did not cont. in Post-Ext Phase       | 1 <sup>[4]</sup>                        | 2 <sup>[5]</sup>                         | 0 <sup>[6]</sup> |

|  |    |    |    |
|--|----|----|----|
| 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:<br>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:<br>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:<br>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<br>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<br>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<br>Units: Subjects          |                                      |                                       |             |
| Female  | 53                                   | 65                                    | 58          |
| Male  | 64                                   | 65                                    | 61          |
| Race/Ethnicity, Customized<br>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<br>Units: kg                           |                                      |                                       |             |
| arithmetic mean                               | 38.69                                | 40.75                                 | 40.50       |
| standard deviation                            | ± 22.802                             | ± 27.267                              | ± 24.923    |
| Height<br>Units: cm                           |                                      |                                       |             |
| arithmetic mean                               | 135.65                               | 136.25                                | 135.67      |
| standard deviation                            | ± 26.171                             | ± 28.234                              | ± 27.097    |
| Body surface area                             |                                      |                                       |             |

|  |                  |                  |                  |
|--|------------------|------------------|------------------|
| Units: m <sup>2</sup><br>arithmetic mean<br>standard deviation                       | 1.18<br>± 0.437  | 1.20<br>± 0.501  | 1.20<br>± 0.176  |
| Body mass index<br>Units: kg/m <sup>2</sup><br>arithmetic mean<br>standard deviation | 19.29<br>± 5.283 | 19.56<br>± 6.233 | 19.55<br>± 5.689 |

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



## End points

### End points reporting groups

|   |                                       |
|---|---------------------------------------|
| Reporting group title   | Everolimus LT target of 3 to 7 ng/mL  |
| Reporting group description:<br>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:<br>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:<br>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:<br>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:<br>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:<br>Observed TN-Cmin concentration 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:<br>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:<br>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:<br>Antiepileptic drug   |                                       |
| Subject analysis set title  | Carbamazepine                         |
| Subject analysis set type   | Sub-group analysis                    |
| Subject analysis set description:<br>Antiepileptic drug   |                                       |
| Subject analysis set title  | Cobazam                               |
| Subject analysis set type   | Sub-group analysis                    |
| Subject analysis set description:<br>antiepileptic drug   |                                       |
| Subject analysis set title  | N-desmethylclobazam                   |
| Subject analysis set type   | Sub-group analysis                    |
| Subject analysis set description:<br>antiepileptic drug   |                                       |

|  |                                       |
|--|---------------------------------------|
| Subject analysis set title   | Topiramate                            |
| Subject analysis set type  | Sub-group analysis                    |
| Subject analysis set description:<br>antiepileptic drug  |                                       |
| Subject analysis set title   | TRI477                                |
| Subject analysis set type  | Sub-group analysis                    |
| Subject analysis set description:<br>antiepileptic drug  |                                       |
| Subject analysis set title   | TRI476                                |
| Subject analysis set type  | Sub-group analysis                    |
| Subject analysis set description:<br>antiepileptic drug  |                                       |
| Subject analysis set title   | Clonazepam                            |
| Subject analysis set type  | Sub-group analysis                    |
| Subject analysis set description:<br>antiepileptic drug  |                                       |
| Subject analysis set title   | Zonisamide                            |
| Subject analysis set type  | Sub-group analysis                    |
| Subject analysis set description:<br>antiepileptic drug  |                                       |
| Subject analysis set title   | Phenobarbital                         |
| Subject analysis set type  | Sub-group analysis                    |
| Subject analysis set description:<br>antiepileptic drug  |                                       |
| Subject analysis set title   | Phenytoin                             |
| Subject analysis set type  | Sub-group analysis                    |
| Subject analysis set description:<br>antiepileptic drug  |                                       |
| Subject analysis set title   | Everolimus Long Term Evaluation       |
| Subject analysis set type  | Modified intention-to-treat           |
| Subject analysis set description:<br>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:<br>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:<br>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:<br>Baseline (8-week period before randomization), Week 7 to 18 (12-week maintenance period of the core phase)   |   |

| <b>End point values</b>          | 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

| <b>Statistical analysis title</b>       | 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  |

| <b>Statistical analysis title</b>       | 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**

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | 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  |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | 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   |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | 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  $\geq 25\%$  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

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | 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   |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | 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 ( $\leq$  -25% (exacerbation);  $>$  -25% to  $<$  25% (no change);  $\geq$  25% to  $<$  50%;  $\geq$  50% to  $<$  75%;  $\geq$  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<br>target of 3 to 7<br>ng/mL | Everolimus HT<br>target of 9 to<br>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<br>target of 3 to 7<br>ng/mL | Everolimus HT<br>target of 9 to<br>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                            |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | 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

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | 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   |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | 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 |
|-----------------|--|

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 ( $\pm$ 7.06)                    | 6.0 ( $\pm$ 13.83)                    | 4.9 ( $\pm$ 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  $\geq 18$  years**

|                 |  |
|-----------------|--|
| End point title | Core Phase: Change from baseline of Patient-oriented outcomes (PROs) Quality of Life (QoL) questionnaire: QOLIE-31-P patients aged $\geq 18$ 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 ( $\pm$ 15.84)                   | -2.4 ( $\pm$ 17.36)                   | 5.7 ( $\pm$ 17.15) |  |

**Statistical analyses**

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | 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   |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | 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-II)

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

## 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<br>target of 3 to 7<br>ng/mL | Everolimus HT<br>target of 9 to<br>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<br>Long Term<br>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

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

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|                 |  |
|-----------------|--|
| 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

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| 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)             |  |  |  |

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**Statistical analyses**

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No statistical analyses for this end point

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

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|                 |  |
|-----------------|--|
| 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

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| End point values                         | Valporic acid          | Carbamazepine          | Cobazam                | N-desmethyloclobazam   |
|--|------------------------|------------------------|------------------------|------------------------|
| 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

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

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|                 |  |
|-----------------|--|
| 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 |
|-----------------|--|

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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.

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|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

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End point timeframe:

During everolimus treatment from start of everolimus to end of everolimus

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|   |                                 |  |  |  |
|---|---------------------------------|--|--|--|
| <b>End point values</b>                         | 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                               |  |  |  |

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**Statistical analyses**

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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           |

|                                    |                |  |  |
|------------------------------------|----------------|--|--|
| <b>Serious adverse events</b>      | 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           |  |  |
| <b>Investigations</b>                                 |                 |  |  |
| 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           |  |  |
| <b>Injury, poisoning and procedural complications</b> |                 |  |  |
| 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 %

| <b>Non-serious adverse events</b>                     | Everolimus 3-7<br>ng/ml | Everolimus start Ext | Everolimus 9-15<br>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<br>occurrences (all)                                      | 4 / 117 (3.42%)<br>6    | 3 / 114 (2.63%)<br>3    | 12 / 130 (9.23%)<br>29  |
| Nasal congestion<br>subjects affected / exposed<br>occurrences (all)                  | 4 / 117 (3.42%)<br>4    | 1 / 114 (0.88%)<br>1    | 7 / 130 (5.38%)<br>8    |
| Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)                | 5 / 117 (4.27%)<br>8    | 5 / 114 (4.39%)<br>5    | 10 / 130 (7.69%)<br>12  |
| Rhinorrhoea<br>subjects affected / exposed<br>occurrences (all)                       | 10 / 117 (8.55%)<br>20  | 3 / 114 (2.63%)<br>4    | 9 / 130 (6.92%)<br>11   |
| Psychiatric disorders   |                         |                         |                         |
| Aggression<br>subjects affected / exposed<br>occurrences (all)                        | 5 / 117 (4.27%)<br>5    | 1 / 114 (0.88%)<br>3    | 8 / 130 (6.15%)<br>8    |
| Agitation<br>subjects affected / exposed<br>occurrences (all)                         | 7 / 117 (5.98%)<br>8    | 2 / 114 (1.75%)<br>2    | 1 / 130 (0.77%)<br>1    |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)                          | 8 / 117 (6.84%)<br>11   | 2 / 114 (1.75%)<br>2    | 8 / 130 (6.15%)<br>9    |
| Irritability<br>subjects affected / exposed<br>occurrences (all)                      | 5 / 117 (4.27%)<br>6    | 7 / 114 (6.14%)<br>7    | 4 / 130 (3.08%)<br>4    |
| Investigations  |                         |                         |                         |
| Blood cholesterol increased<br>subjects affected / exposed<br>occurrences (all)       | 14 / 117 (11.97%)<br>20 | 17 / 114 (14.91%)<br>19 | 20 / 130 (15.38%)<br>30 |
| Blood triglycerides increased<br>subjects affected / exposed<br>occurrences (all)     | 5 / 117 (4.27%)<br>6    | 6 / 114 (5.26%)<br>7    | 10 / 130 (7.69%)<br>16  |
| Low density lipoprotein increased<br>subjects affected / exposed<br>occurrences (all) | 6 / 117 (5.13%)<br>8    | 3 / 114 (2.63%)<br>4    | 8 / 130 (6.15%)<br>13   |
| Weight decreased  |                         |                         |                         |

|  |                        |                      |                      |
|--|------------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all) | 10 / 117 (8.55%)<br>11 | 8 / 114 (7.02%)<br>9 | 7 / 130 (5.38%)<br>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<br>subjects affected / exposed<br>occurrences (all) | 7 / 117 (5.98%)<br>8     | 5 / 114 (4.39%)<br>5     | 10 / 130 (7.69%)<br>14   |
| Aphthous ulcer<br>subjects affected / exposed<br>occurrences (all)       | 11 / 117 (9.40%)<br>21   | 10 / 114 (8.77%)<br>17   | 23 / 130 (17.69%)<br>56  |
| Constipation<br>subjects affected / exposed<br>occurrences (all)         | 9 / 117 (7.69%)<br>9     | 7 / 114 (6.14%)<br>7     | 12 / 130 (9.23%)<br>12   |
| Dental caries<br>subjects affected / exposed<br>occurrences (all)        | 6 / 117 (5.13%)<br>10    | 3 / 114 (2.63%)<br>3     | 2 / 130 (1.54%)<br>2     |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)            | 45 / 117 (38.46%)<br>97  | 30 / 114 (26.32%)<br>57  | 42 / 130 (32.31%)<br>83  |
| Mouth ulceration<br>subjects affected / exposed<br>occurrences (all)     | 36 / 117 (30.77%)<br>157 | 22 / 114 (19.30%)<br>77  | 44 / 130 (33.85%)<br>130 |
| Nausea<br>subjects affected / exposed<br>occurrences (all)               | 6 / 117 (5.13%)<br>8     | 3 / 114 (2.63%)<br>3     | 7 / 130 (5.38%)<br>9     |
| Stomatitis<br>subjects affected / exposed<br>occurrences (all)           | 41 / 117 (35.04%)<br>84  | 41 / 114 (35.96%)<br>120 | 48 / 130 (36.92%)<br>110 |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)             | 28 / 117 (23.93%)<br>109 | 16 / 114 (14.04%)<br>36  | 35 / 130 (26.92%)<br>47  |
| Skin and subcutaneous tissue disorders                                   |                          |                          |                          |
| Acne<br>subjects affected / exposed<br>occurrences (all)                 | 6 / 117 (5.13%)<br>6     | 6 / 114 (5.26%)<br>7     | 14 / 130 (10.77%)<br>17  |
| Alopecia<br>subjects affected / exposed<br>occurrences (all)             | 4 / 117 (3.42%)<br>4     | 2 / 114 (1.75%)<br>2     | 8 / 130 (6.15%)<br>10    |
| Dermatitis   |                          |                          |                          |

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

|  |                |  |  |
|--|----------------|--|--|
| <b>Non-serious adverse events</b>      | Everolimus All |  |  |
| Total subjects affected by non-serious |                |  |  |

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

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

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

|  |                    |  |  |
|--|--------------------|--|--|
| 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