



## Clinical trial results:

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

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

## Summary

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

## Results information

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

## Trial information

### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | CRAD001M2301 |
|-----------------------|--------------|

### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00789828 |
| WHO universal trial number (UTN)   | -           |

Notes:

## Sponsors

|                              |                                                                |
|------------------------------|----------------------------------------------------------------|
| Sponsor organisation name    | Novartis Pharma AG                                             |
| Sponsor organisation address | CH-4002, Basel, Switzerland,                                   |
| Public contact               | Clinical Disclosure Office, Novartis Pharma AG, +41 613241111, |
| Scientific contact           | Clinical Disclosure Office, Novartis Pharma AG, +41 613241111, |

Notes:

## Paediatric regulatory details

|                                                                      |                     |
|----------------------------------------------------------------------|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP)       | Yes                 |
| EMA paediatric investigation plan number(s)                          | EMA-000019-PIP02-07 |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No                  |

|                                                                      |     |
|----------------------------------------------------------------------|-----|
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | Yes |
|----------------------------------------------------------------------|-----|

Notes:

## Results analysis stage

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

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

Notes:

## General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial

Background therapy: -

Evidence for comparator: -

|                                                           |                |
|-----------------------------------------------------------|----------------|
| Actual start date of recruitment                          | 10 August 2009 |
| Long term follow-up planned                               | No             |
| Independent data monitoring committee (IDMC) involvement? | Yes            |

Notes:

## Population of trial subjects

### Subjects enrolled per country

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

Notes:

| <b>Subjects enrolled per age group</b>    |    |
|-------------------------------------------|----|
| In utero                                  | 0  |
| Preterm newborn - gestational age < 37 wk | 0  |
| Newborns (0-27 days)                      | 0  |
| Infants and toddlers (28 days-23 months)  | 13 |
| Children (2-11 years)                     | 61 |
| Adolescents (12-17 years)                 | 27 |
| Adults (18-64 years)                      | 16 |
| From 65 to 84 years                       | 0  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at 24 centres in 10 countries.

### Pre-assignment

Screening details:

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

### Period 1

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

Blinding implementation details:

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

### Arms

|                              |     |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

|                  |                          |
|------------------|--------------------------|
| <b>Arm title</b> | Everolimus (Core period) |
|------------------|--------------------------|

Arm description:

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

|                                        |              |
|----------------------------------------|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Everolimus   |
| Investigational medicinal product code | RAD001       |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

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

|                  |                       |
|------------------|-----------------------|
| <b>Arm title</b> | Placebo (Core period) |
|------------------|-----------------------|

Arm description:

Subjects received oral dose of placebo matching to everolimus daily.

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

Dosage and administration details:

Placebo matched to everolimus was administered daily via oral route.

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

## Period 2

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

Blinding implementation details:

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

## Arms

|           |                               |
|-----------|-------------------------------|
| Arm title | Everolimus (Extension period) |
|-----------|-------------------------------|

Arm description:

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

|                                        |              |
|----------------------------------------|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Everolimus   |
| Investigational medicinal product code | RAD001       |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

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

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

|                         |   |
|-------------------------|---|
| Administrative problems | 7 |
| Lost to follow-up       | 3 |

## Baseline characteristics

### Reporting groups

|                       |                          |
|-----------------------|--------------------------|
| Reporting group title | Everolimus (Core period) |
|-----------------------|--------------------------|

Reporting group description:

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

|                       |                       |
|-----------------------|-----------------------|
| Reporting group title | Placebo (Core period) |
|-----------------------|-----------------------|

Reporting group description:

Subjects received oral dose of placebo matching to everolimus daily.

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

## End points

### End points reporting groups

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

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

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

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

### Statistical analyses

|                            |                                                   |
|----------------------------|---------------------------------------------------|
| Statistical analysis title | Response rate difference during core study period |
|----------------------------|---------------------------------------------------|



**Statistical analysis description:**

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

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

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


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

**End point description:**

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

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

**End point timeframe:**

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

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

**Statistical analyses**

No statistical analyses for this end point

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**Secondary: Time to SEGA progression**


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|                 |                          |
|-----------------|--------------------------|
| End point title | Time to SEGA progression |
|-----------------|--------------------------|

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**End point description:**

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

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

**End point timeframe:**

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

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

**Notes:**

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

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

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

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Time to SEGA response**

|                 |                                      |
|-----------------|--------------------------------------|
| End point title | Time to SEGA response <sup>[4]</sup> |
|-----------------|--------------------------------------|

**End point description:**

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

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

**End point timeframe:**

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

**Notes:**

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

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

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

## Statistical analyses

No statistical analyses for this end point

## Secondary: Duration of SEGA response

|                 |                                          |
|-----------------|------------------------------------------|
| End point title | Duration of SEGA response <sup>[5]</sup> |
|-----------------|------------------------------------------|

End point description:

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

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

End point timeframe:

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

Notes:

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

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

Notes:

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

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

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to SEGA worsening

|                 |                        |
|-----------------|------------------------|
| End point title | Time to SEGA worsening |
|-----------------|------------------------|

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**End point description:**

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

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

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**End point timeframe:**

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

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

**Notes:**

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

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

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**Statistical analyses**

No statistical analyses for this end point

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

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

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**End point description:**

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

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

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**End point timeframe:**

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

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

## Statistical analyses

No statistical analyses for this end point

## Secondary: Duration of skin lesion response

|                 |                                                  |
|-----------------|--------------------------------------------------|
| End point title | Duration of skin lesion response <sup>[10]</sup> |
|-----------------|--------------------------------------------------|

End point description:

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

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

End point timeframe:

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

Notes:

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

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

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

Notes:

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

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

## Statistical analyses

No statistical analyses for this end point

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

|                 |                                                                           |
|-----------------|---------------------------------------------------------------------------|
| End point title | Everolimus blood concentration (C2h) at 2 hours post dose <sup>[13]</sup> |
|-----------------|---------------------------------------------------------------------------|

End point description:

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

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

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

End point timeframe:

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

Notes:

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

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

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

## Statistical analyses

No statistical analyses for this end point

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

|                 |                                                                                     |
|-----------------|-------------------------------------------------------------------------------------|
| End point title | Everolimus trough concentrations (Cmin) at 24 hours after last dose <sup>[14]</sup> |
|-----------------|-------------------------------------------------------------------------------------|

End point description:

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

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

End point timeframe:

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

Notes:

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

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

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

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of subjects with renal impairment during core period

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

End point description:

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

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

End point timeframe:

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

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

### Statistical analyses

No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

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

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 17.0 |
|--------------------|------|

### Reporting groups

|                       |                                      |
|-----------------------|--------------------------------------|
| Reporting group title | Everolimus (Core + Extension period) |
|-----------------------|--------------------------------------|

Reporting group description:

Subjects who recieved Everolimu both in core and extension period.

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

Reporting group description:

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

|                       |                                     |
|-----------------------|-------------------------------------|
| Reporting group title | Placebo (Core period, No extension) |
|-----------------------|-------------------------------------|

Reporting group description:

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

| Serious adverse events                               | Everolimus (Core + Extension period) | Placebo (Core) + Everolimus (Extention) | Placebo (Core period, No extension) |
|------------------------------------------------------|--------------------------------------|-----------------------------------------|-------------------------------------|
| Total subjects affected by serious adverse events    |                                      |                                         |                                     |
| subjects affected / exposed                          | 33 / 78 (42.31%)                     | 17 / 33 (51.52%)                        | 3 / 6 (50.00%)                      |
| number of deaths (all causes)                        | 0                                    | 1                                       | 0                                   |
| number of deaths resulting from adverse events       | 0                                    | 0                                       | 0                                   |
| Vascular disorders                                   |                                      |                                         |                                     |
| Raynaud's phenomenon                                 |                                      |                                         |                                     |
| subjects affected / exposed                          | 0 / 78 (0.00%)                       | 0 / 33 (0.00%)                          | 1 / 6 (16.67%)                      |
| occurrences causally related to treatment / all      | 0 / 0                                | 0 / 0                                   | 0 / 1                               |
| deaths causally related to treatment / all           | 0 / 0                                | 0 / 0                                   | 0 / 0                               |
| General disorders and administration site conditions |                                      |                                         |                                     |
| Pyrexia                                              |                                      |                                         |                                     |
| subjects affected / exposed                          | 3 / 78 (3.85%)                       | 2 / 33 (6.06%)                          | 1 / 6 (16.67%)                      |
| occurrences causally related to treatment / all      | 5 / 7                                | 1 / 2                                   | 0 / 1                               |
| deaths causally related to treatment / all           | 0 / 0                                | 0 / 0                                   | 0 / 0                               |
| Immune system disorders                              |                                      |                                         |                                     |

|                                                 |                |                |               |
|-------------------------------------------------|----------------|----------------|---------------|
| Hypersensitivity                                |                |                |               |
| subjects affected / exposed                     | 1 / 78 (1.28%) | 0 / 33 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Respiratory, thoracic and mediastinal disorders |                |                |               |
| Asphyxia                                        |                |                |               |
| subjects affected / exposed                     | 0 / 78 (0.00%) | 1 / 33 (3.03%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0         |
| Pneumonia aspiration                            |                |                |               |
| subjects affected / exposed                     | 1 / 78 (1.28%) | 0 / 33 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Pneumothorax                                    |                |                |               |
| subjects affected / exposed                     | 1 / 78 (1.28%) | 0 / 33 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Pulmonary pneumatocele                          |                |                |               |
| subjects affected / exposed                     | 0 / 78 (0.00%) | 1 / 33 (3.03%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Tonsillar hypertrophy                           |                |                |               |
| subjects affected / exposed                     | 1 / 78 (1.28%) | 0 / 33 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Psychiatric disorders                           |                |                |               |
| Affective disorder                              |                |                |               |
| subjects affected / exposed                     | 1 / 78 (1.28%) | 1 / 33 (3.03%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Agitation                                       |                |                |               |
| subjects affected / exposed                     | 1 / 78 (1.28%) | 0 / 33 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| Investigations                                  |                |                |                |
| Blood alkaline phosphatase increased            |                |                |                |
| subjects affected / exposed                     | 0 / 78 (0.00%) | 1 / 33 (3.03%) | 0 / 6 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Injury, poisoning and procedural complications  |                |                |                |
| Accidental overdose                             |                |                |                |
| subjects affected / exposed                     | 1 / 78 (1.28%) | 0 / 33 (0.00%) | 0 / 6 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Foreign body aspiration                         |                |                |                |
| subjects affected / exposed                     | 1 / 78 (1.28%) | 0 / 33 (0.00%) | 0 / 6 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Procedural pain                                 |                |                |                |
| subjects affected / exposed                     | 1 / 78 (1.28%) | 0 / 33 (0.00%) | 0 / 6 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Nervous system disorders                        |                |                |                |
| Ataxia                                          |                |                |                |
| subjects affected / exposed                     | 1 / 78 (1.28%) | 0 / 33 (0.00%) | 0 / 6 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Complex partial seizures                        |                |                |                |
| subjects affected / exposed                     | 1 / 78 (1.28%) | 0 / 33 (0.00%) | 0 / 6 (0.00%)  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Convulsion                                      |                |                |                |
| subjects affected / exposed                     | 4 / 78 (5.13%) | 1 / 33 (3.03%) | 2 / 6 (33.33%) |
| occurrences causally related to treatment / all | 0 / 6          | 0 / 1          | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Drooling                                        |                |                |                |

|                                                 |                |                |               |
|-------------------------------------------------|----------------|----------------|---------------|
| subjects affected / exposed                     | 1 / 78 (1.28%) | 0 / 33 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Epilepsy                                        |                |                |               |
| subjects affected / exposed                     | 2 / 78 (2.56%) | 0 / 33 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Febrile convulsion                              |                |                |               |
| subjects affected / exposed                     | 1 / 78 (1.28%) | 0 / 33 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Grand mal convulsion                            |                |                |               |
| subjects affected / exposed                     | 1 / 78 (1.28%) | 0 / 33 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Headache                                        |                |                |               |
| subjects affected / exposed                     | 0 / 78 (0.00%) | 1 / 33 (3.03%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Partial seizures                                |                |                |               |
| subjects affected / exposed                     | 1 / 78 (1.28%) | 0 / 33 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Status epilepticus                              |                |                |               |
| subjects affected / exposed                     | 2 / 78 (2.56%) | 1 / 33 (3.03%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 1          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Blood and lymphatic system disorders            |                |                |               |
| Anaemia                                         |                |                |               |
| subjects affected / exposed                     | 0 / 78 (0.00%) | 1 / 33 (3.03%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Lymphadenopathy                                 |                |                |               |

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

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

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

|                                                 |                |                |               |
|-------------------------------------------------|----------------|----------------|---------------|
| subjects affected / exposed                     | 1 / 78 (1.28%) | 0 / 33 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Herpes zoster                                   |                |                |               |
| subjects affected / exposed                     | 0 / 78 (0.00%) | 1 / 33 (3.03%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Infected bites                                  |                |                |               |
| subjects affected / exposed                     | 1 / 78 (1.28%) | 0 / 33 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Influenza                                       |                |                |               |
| subjects affected / exposed                     | 1 / 78 (1.28%) | 0 / 33 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Laryngitis                                      |                |                |               |
| subjects affected / exposed                     | 1 / 78 (1.28%) | 0 / 33 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Mastoiditis                                     |                |                |               |
| subjects affected / exposed                     | 1 / 78 (1.28%) | 0 / 33 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Meningitis viral                                |                |                |               |
| subjects affected / exposed                     | 0 / 78 (0.00%) | 1 / 33 (3.03%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Nasopharyngitis                                 |                |                |               |
| subjects affected / exposed                     | 1 / 78 (1.28%) | 0 / 33 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Otitis media                                    |                |                |               |



|                                                 |                  |                 |                |
|-------------------------------------------------|------------------|-----------------|----------------|
| subjects affected / exposed                     | 2 / 78 (2.56%)   | 0 / 33 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences causally related to treatment / all | 1 / 2            | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0          |
| Parainfluenzae virus infection                  |                  |                 |                |
| subjects affected / exposed                     | 1 / 78 (1.28%)   | 0 / 33 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0          |
| Pertussis                                       |                  |                 |                |
| subjects affected / exposed                     | 0 / 78 (0.00%)   | 1 / 33 (3.03%)  | 0 / 6 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0          |
| Pneumonia                                       |                  |                 |                |
| subjects affected / exposed                     | 11 / 78 (14.10%) | 5 / 33 (15.15%) | 1 / 6 (16.67%) |
| occurrences causally related to treatment / all | 9 / 14           | 2 / 5           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0          |
| Respiratory tract infection viral               |                  |                 |                |
| subjects affected / exposed                     | 1 / 78 (1.28%)   | 1 / 33 (3.03%)  | 0 / 6 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1            | 1 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0          |
| Sinusitis                                       |                  |                 |                |
| subjects affected / exposed                     | 0 / 78 (0.00%)   | 1 / 33 (3.03%)  | 0 / 6 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0          |
| Tonsillitis                                     |                  |                 |                |
| subjects affected / exposed                     | 1 / 78 (1.28%)   | 0 / 33 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0          |
| Tooth abscess                                   |                  |                 |                |
| subjects affected / exposed                     | 0 / 78 (0.00%)   | 1 / 33 (3.03%)  | 0 / 6 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0          |
| Upper respiratory tract infection               |                  |                 |                |

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

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

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

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

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

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

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

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

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



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

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

|                                                                                       |                        |                       |                     |
|---------------------------------------------------------------------------------------|------------------------|-----------------------|---------------------|
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 23 / 78 (29.49%)<br>35 | 7 / 33 (21.21%)<br>13 | 3 / 6 (50.00%)<br>3 |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)           | 7 / 78 (8.97%)<br>13   | 1 / 33 (3.03%)<br>4   | 0 / 6 (0.00%)<br>0  |
| Varicella<br>subjects affected / exposed<br>occurrences (all)                         | 4 / 78 (5.13%)<br>4    | 0 / 33 (0.00%)<br>0   | 0 / 6 (0.00%)<br>0  |
| Viral infection<br>subjects affected / exposed<br>occurrences (all)                   | 6 / 78 (7.69%)<br>9    | 3 / 33 (9.09%)<br>3   | 0 / 6 (0.00%)<br>0  |
| Vulvovaginal mycotic infection<br>subjects affected / exposed<br>occurrences (all)    | 1 / 78 (1.28%)<br>1    | 1 / 33 (3.03%)<br>1   | 1 / 6 (16.67%)<br>1 |
| Metabolism and nutrition disorders                                                    |                        |                       |                     |
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all)                | 12 / 78 (15.38%)<br>16 | 6 / 33 (18.18%)<br>7  | 0 / 6 (0.00%)<br>0  |
| Dehydration<br>subjects affected / exposed<br>occurrences (all)                       | 2 / 78 (2.56%)<br>2    | 1 / 33 (3.03%)<br>1   | 2 / 6 (33.33%)<br>2 |
| Hypercholesterolaemia<br>subjects affected / exposed<br>occurrences (all)             | 11 / 78 (14.10%)<br>12 | 3 / 33 (9.09%)<br>3   | 0 / 6 (0.00%)<br>0  |
| Hyperlipidaemia<br>subjects affected / exposed<br>occurrences (all)                   | 6 / 78 (7.69%)<br>6    | 0 / 33 (0.00%)<br>0   | 0 / 6 (0.00%)<br>0  |
| Hypertriglyceridaemia<br>subjects affected / exposed<br>occurrences (all)             | 4 / 78 (5.13%)<br>7    | 2 / 33 (6.06%)<br>2   | 0 / 6 (0.00%)<br>0  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 11 August 2009   | The requirement of target lesion volume increase above the baseline value for defining progression was added. The exclusion criterion of prior brain surgery was removed, and renal disease was allowed. Skin lesion response scans were allowed to carry out in 12 weeks after initial response and the screening period was increased from 14 to 21 days                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 02 April 2010    | <ul style="list-style-type: none"><li>- Target everolimus concentration range was modified from 10-15 ng/mL to 5-15 ng/mL, two additional dose levels (10.67 mg/m<sup>2</sup> and 14.22 mg/m<sup>2</sup>) were added.</li><li>- Stricter guidance with respect to changes in endocrine hormone levels and hepatitis virus screening was implemented.</li><li>- The screening period for the study was extended from 21 to 28 days.</li><li>- Added endocrine blood testing (testosterone, LH, FSH and Estradiol) at screening and subsequent timepoints according to age and gender</li><li>- Added Tanner staging to assess sexual maturation at screening and subsequent timepoints according to age</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 11 January 2011  | Evaluation of any potential effects of everolimus on growth and development in the pediatric population was allowed. The definition and safety recommendations concerning hepatitis B virus (HBV) reactivation and hepatitis C virus (HCV) flare were modified.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 23 February 2011 | All subjects have endocrine testing at baseline or at their next scheduled visit (if no prior endocrine testing had been done). Endocrine blood sampling was completed annually until the subject's 10th birthday and every 12 weeks thereafter.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 05 March 2012    | As part of this amendment, a full pharmacokinetic (PK) profile was collected from subjects currently active in the study. New PK collection time-points were added.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 22 August 2012   | <ul style="list-style-type: none"><li>- Changed inclusion criteria to include highly effective contraceptive measures instead of adequate contraceptive measures.</li><li>- Added secondary amenorrhea as an identified risk of study drug. Added information on management of secondary amenorrhea.</li><li>- Added detailed description of highly effective contraceptive measures.</li><li>- Added completion of hormone evaluations when amenorrhea is seen between scheduled assessments.</li><li>- Revised 2 tables:<ul style="list-style-type: none"><li>- Urine pregnancy testing frequency increased from every 12 weeks to every 4 weeks.</li><li>- Serum pregnancy test added to End of Treatment evaluation.</li><li>- Additional menstrual history and pregnancy history information collected. Will conduct monthly monitoring of menstrual status.</li><li>- Added collection of biological parental height to assist us in the evaluation of patient's growth and development.</li></ul></li><li>- Section revised to include<ul style="list-style-type: none"><li>- Urine pregnancy testing frequency increased from every 12 weeks to every 4 weeks. Serum pregnancy test added to End of Treatment evaluation.</li><li>- Parental height subsection added. Data will be used to evaluate patient's growth and development.</li><li>- Revised endocrine testing section to include reproductive history. Additional medical information on reproductive history will be collected.</li><li>- Additional safety language for pregnancies added</li><li>- Added data collection language regarding the results from at home urine pregnancy to be recorded on patient diaries for source documentation only.</li></ul></li></ul> |

|                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 15 January 2013 | <p>- In the section, Amendment (date 22-Aug-2012), Changes to the protocol, the following paragraph is deleted: "This amendment is required for patient safety (i.e. necessary to eliminate immediate hazards to the trial patients International Conference on Harmonization GCP 3.3.8). Therefore it will be implemented prior to IRB/IEC approval, but will be sent for approval as well."</p> <p>- In the section, Amendment (date 22-Aug-2012), Changes to the protocol, the following paragraph is added: "The changes described in this amended protocol require IRB/EC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol."</p> |
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Notes:

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## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

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

Notes: