



## Clinical trial results:

### A Phase II Study of RAD001 in the Treatment of Patients with Plexiform Neurofibromas (PN) associated with Neurofibromatosis Type 1 (NF1)

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           | 2016-001563-36 |
| Trial protocol           | Outside EU/EEA |
| Global end of trial date | 26 April 2015  |

## Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 06 July 2018 |
| First version publication date | 06 July 2018 |

## Trial information

### Trial identification

|                       |               |
|-----------------------|---------------|
| Sponsor protocol code | CRAD001MIL04T |
|-----------------------|---------------|

### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01365468 |
| WHO universal trial number (UTN)   | -           |

Notes:

## Sponsors

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

Notes:

## Paediatric regulatory details

|  |     |
|--|-----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No  |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No  |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | Yes |

Notes:

## Results analysis stage

|  |               |
|--|---------------|
| Analysis stage                                       | Final         |
| Date of interim/final analysis                       | 26 April 2015 |
| Is this the analysis of the primary completion data? | No            |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 26 April 2015 |
| Was the trial ended prematurely?                     | Yes           |

Notes:

## General information about the trial

Main objective of the trial:

-To determine whether the mTOR inhibitor everolimus, administrated orally daily on a continuous dosing schedule:

a) Increases time to disease progression (TTP) based on volumetric MRI measurements in children and adults with NF1 and inoperable documented progressive PN (Stratum 1).

b) Results in objective radiographic responses based on volumetric MRI measurements in children and adults with NF1 and inoperable PN in the absence of documented radiographic progression at the study entry (Stratum 2).

-To evaluate the tolerability and toxicity of chronic everolimus administration in this patient population as assessed by the NCI Common Toxicity Criteria, version 4.0.

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                          | 24 April 2012 |
| Long term follow-up planned                               | No            |
| Independent data monitoring committee (IDMC) involvement? | No            |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |           |
|--------------------------------------|-----------|
| Country: Number of subjects enrolled | Israel: 9 |
| Worldwide total number of subjects   | 9         |
| EEA total number of subjects         | 0         |

Notes:

### Subjects enrolled per age group

|   |   |
|---|---|
| In utero                                  | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days)                      | 0 |
| Infants and toddlers (28 days-23 months)  | 0 |

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

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Total of 9 patients were enrolled to either Stratum 1 (N=4) or Stratum 2 (N=5)

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall Study (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Not applicable                 |
| Blinding used                | Not blinded                    |

### Arms

|                              |           |
|------------------------------|-----------|
| Are arms mutually exclusive? | Yes       |
| <b>Arm title</b>             | Stratum 1 |

Arm description:

Adults and children with neurofibromatosis type 1 (NF1) and inoperable plexiform neurofibromas (PN) with the potential to cause significant morbidity with documented progressive PN prior to study entry were enrolled in this stratum. Enrolled patients received everolimus (RAD001) in an open label manner. Recommended starting dose of everolimus depend on body surface area, starting from 2.5 mg once daily to 7.5 mg once daily.

|  |              |
|--|--------------|
| 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:

oral daily dosing of tablet starting with 2.5 mg

|                  |           |
|------------------|-----------|
| <b>Arm title</b> | Stratum 2 |
|------------------|-----------|

Arm description:

Adults and children with neurofibromatosis type 1 (NF1) and inoperable plexiform neurofibromas (PN) with the potential to cause significant morbidity that do not have documented progression of the PN at the time of study entry were enrolled in this stratum. Enrolled patients received everolimus (RAD001) in an open label manner. Recommended starting dose of everolimus depend on body surface area, starting from 2.5 mg once daily to 7.5 mg once daily.

|  |              |
|--|--------------|
| 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:

oral daily dosing of tablet starting with 2.5 mg

| <b>Number of subjects in period 1</b> | Stratum 1 | Stratum 2 |
|---------------------------------------|-----------|-----------|
| Started                               | 4         | 5         |
| Completed                             | 0         | 5         |
| Not completed                         | 4         | 0         |
| Physician decision                    | 1         | -         |
| Disease progression                   | 1         | -         |
| Lost to follow-up                     | 2         | -         |

## Baseline characteristics

### Reporting groups

|  |           |
|--|-----------|
| Reporting group title  | Stratum 1 |
| Reporting group description:   |           |
| Adults and children with neurofibromatosis type 1 (NF1) and inoperable plexiform neurofibromas (PN) with the potential to cause significant morbidity with documented progressive PN prior to study entry were enrolled in this stratum. Enrolled patients received everolimus (RAD001) in an open label manner. Recommended starting dose of everolimus depend on body surface area, starting from 2.5 mg once daily to 7.5 mg once daily.                          |           |
| Reporting group title  | Stratum 2 |
| Reporting group description:   |           |
| Adults and children with neurofibromatosis type 1 (NF1) and inoperable plexiform neurofibromas (PN) with the potential to cause significant morbidity that do not have documented progression of the PN at the time of study entry were enrolled in this stratum. Enrolled patients received everolimus (RAD001) in an open label manner. Recommended starting dose of everolimus depend on body surface area, starting from 2.5 mg once daily to 7.5 mg once daily. |           |

| Reporting group values                             | Stratum 1 | Stratum 2 | Total |
|--|-----------|-----------|-------|
| Number of subjects                                 | 4         | 5         | 9     |
| Age categorical                                    |           |           |       |
| Units: Subjects                                    |           |           |       |
| In utero   |           |           | 0     |
| Preterm newborn infants (gestational age < 37 wks) |           |           | 0     |
| Newborns (0-27 days)                               |           |           | 0     |
| Infants and toddlers (28 days-23 months)           |           |           | 0     |
| Children (2-11 years)                              |           |           | 0     |
| Adolescents (12-17 years)                          |           |           | 0     |
| Adults (18-64 years)                               |           |           | 0     |
| From 65-84 years                                   |           |           | 0     |
| 85 years and over                                  |           |           | 0     |
| Age Continuous                                     |           |           |       |
| Units: Years                                       |           |           |       |
| arithmetic mean                                    | 22.7      | 16.9      |       |
| standard deviation                                 | ± 14.3    | ± 9.8     | -     |
| Gender, Male/Female                                |           |           |       |
| Units: Participants                                |           |           |       |
| Female   | 3         | 1         | 4     |
| Male   | 1         | 4         | 5     |

## End points

### End points reporting groups

|  |           |
|--|-----------|
| Reporting group title  | Stratum 1 |
| Reporting group description:   |           |
| Adults and children with neurofibromatosis type 1 (NF1) and inoperable plexiform neurofibromas (PN) with the potential to cause significant morbidity with documented progressive PN prior to study entry were enrolled in this stratum. Enrolled patients received everolimus (RAD001) in an open label manner. Recommended starting dose of everolimus depend on body surface area, starting from 2.5 mg once daily to 7.5 mg once daily.                          |           |
| Reporting group title  | Stratum 2 |
| Reporting group description:   |           |
| Adults and children with neurofibromatosis type 1 (NF1) and inoperable plexiform neurofibromas (PN) with the potential to cause significant morbidity that do not have documented progression of the PN at the time of study entry were enrolled in this stratum. Enrolled patients received everolimus (RAD001) in an open label manner. Recommended starting dose of everolimus depend on body surface area, starting from 2.5 mg once daily to 7.5 mg once daily. |           |

### Primary: Time to disease progression (TTP) based on change in volumetric MRI measurements in children and adults (In Stratum I only)

|                 |   |
|-----------------|---|
| End point title | Time to disease progression (TTP) based on change in volumetric MRI measurements in children and adults (In Stratum I only) <sup>[1][2]</sup> |
|-----------------|---|

#### End point description:

This endpoint was planned to be analyzed for only Stratum 1 patients. Progression of disease defined as a  $\geq 20\%$  increase in the volume (by volumetric MRI) of at least one of the index plexiform neurofibromas (PN) compared to the pretreatment volume measured prior to the start of the current treatment phase. The Full Analysis Set (FAS) consisted of all enrolled patients. Median was not achieved because only one progression event occurred. The system does not accept "NA" for "Not available" or "Not achievable" data, not it allows user to leave the data field blank. To avoid system error, 9999.9 is used as placeholder.

|  |         |
|--|---------|
| End point type   | Primary |
| End point timeframe:   |         |
| Screening, after course #6, #12, #18, #24, End of Treatment(1 course=28days) |         |

#### Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned for this endpoint.

[2] - 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: This primary endpoint was only planned to assess Stratum 1 patients.

| End point values                 | Stratum 1                  |  |  |  |
|----------------------------------|----------------------------|--|--|--|
| Subject group type               | Reporting group            |  |  |  |
| Number of subjects analysed      | 4                          |  |  |  |
| Units: Days                      |                            |  |  |  |
| median (confidence interval 95%) | 9999.9 (-9999.9 to 9999.9) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of patients with objective radiographic responses based on volumetric MRI measurements (In Stratum 2 Only)

|                 |   |
|-----------------|---|
| End point title | Number of patients with objective radiographic responses based on volumetric MRI measurements (In Stratum 2 Only) <sup>[3][4]</sup> |
|-----------------|---|

End point description:

Response was assessed at the time that a follow up volumetric MRI scan is performed (after course 6 and then every 6 months and at the end of treatment). - Complete response (CR): complete resolution of all measurable or palpable PN for  $\geq 28$ days and no appearance of new lesions. - Partial response (PR): A  $\geq 20\%$  reduction in the sum of the volume of all index PN lesions for  $\geq 28$ days. - Stable disease (SD): A  $< 20\%$  increase and  $< 20\%$  decrease in the sum of the volume of all index PN lesions for  $\geq 28$ days.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Screening, after course #6, then every 6 months and end of treatment(1 course=28days)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned for this endpoint.

[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: This primary endpoint was only planned to assess Stratum 2 patients.

| End point values            | Stratum 2       |  |  |  |
|-----------------------------|-----------------|--|--|--|
| Subject group type          | Reporting group |  |  |  |
| Number of subjects analysed | 5               |  |  |  |
| Units: Patients             |                 |  |  |  |
| Complete Response           | 0               |  |  |  |
| Partial Response            | 0               |  |  |  |
| Stable Disease              | 5               |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of patients with adverse events assessed by Common Toxicity Criteria for Adverse Events (CTCAE) V.04

|                 |  |
|-----------------|--|
| End point title | Number of patients with adverse events assessed by Common Toxicity Criteria for Adverse Events (CTCAE) V.04 <sup>[5]</sup> |
|-----------------|--|

End point description:

Adverse events were assessed according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0. If CTCAE grading does not exist for an adverse event, the severity of mild,



moderate, severe, and life-threatening, corresponding to grades 1 - 4 respectively, were used. CTCAE grade 5 (death) was not used in this study.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From the time ICF was signed until 28 days after End of Treatment (up to a maximum of 25 months)

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned for this endpoint.

| End point values            | Stratum 1       | Stratum 2       |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 4               | 5               |  |  |
| Units: Patients             |                 |                 |  |  |
| At least one Grade 1 AE     | 4               | 5               |  |  |
| At least one Grade 2 AE     | 4               | 5               |  |  |
| At least one Grade 3 AE     | 1               | 0               |  |  |
| At least one Grade 4 AE     | 1               | 0               |  |  |

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Number of patients with clinical response

|                 |   |
|-----------------|---|
| End point title | Number of patients with clinical response |
|-----------------|---|

End point description:

Clinical response is defined as improvement of function, performance status, or decrease in PN related pain persisting for at least 28 days on treatment.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Screening, Day 1, after course #3, #6, #12, #18, #24, End of Treatment (1 course = 28 days)

| End point values            | Stratum 1        | Stratum 2        |  |  |
|-----------------------------|------------------|------------------|--|--|
| Subject group type          | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed | 0 <sup>[6]</sup> | 0 <sup>[7]</sup> |  |  |
| Units: Patients             |                  |                  |  |  |

Notes:

[6] - Trial was terminated with only a few patients enrolled. Hence no statistical analysis was done

[7] - Trial was terminated with only a few patients enrolled. Hence no statistical analysis was done

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Physician's Global Assessment of Clinical Condition (PGA) of skin lesions

|   |   |
|---|---|
| End point title   | Physician's Global Assessment of Clinical Condition (PGA) of skin lesions |
| End point description:  |   |
| The Physician's Global Assessment of Clinical Condition (PGA) is a 7-point grading scale for the investigator's assessment of the overall extent of improvement or worsening of the patient's skin disease as compared to baseline. Responses must be confirmed by at least two assessments separated in time by at least 4 weeks. The grading ranges from 0 to 6; 0 is Completely clear where as 6 is for worse condition. A complete clinical response (CCR) requires a grading of 0 indicating the absence of disease (histological confirmation is not required). Grades 1, 2, and 3 constitute partial response, indicating improvement of at least 50 percent, but less than 100 percent improvement. |   |
| End point type  | Other pre-specified   |
| End point timeframe:  |   |
| Screening, after course #3, #6, #12, #18, #24, End of Treatment (1 course = 28 days)  |   |

| End point values                     | Stratum 1        | Stratum 2        |  |  |
|--------------------------------------|------------------|------------------|--|--|
| Subject group type                   | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed          | 0 <sup>[8]</sup> | 0 <sup>[9]</sup> |  |  |
| Units: Unit on scale                 |                  |                  |  |  |
| arithmetic mean (standard deviation) | ()               | ()               |  |  |

Notes:

[8] - Trial was terminated with only a few patients enrolled. Hence no statistical analysis was done

[9] - Trial was terminated with only a few patients enrolled. Hence no statistical analysis was done

### 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 Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit.

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 17.1   |

### Reporting groups

|                       |           |
|-----------------------|-----------|
| Reporting group title | Stratum 2 |
|-----------------------|-----------|

Reporting group description:

Adults and children with neurofibromatosis type 1 (NF1) and inoperable plexiform neurofibromas (PN) with the potential to cause significant morbidity that do not have documented progression of the PN at the time of study entry were enrolled in this stratum. Enrolled patients received everolimus (RAD001) in an open label manner. Recommended starting dose of everolimus depend on body surface area, starting from 2.5 mg once daily to 7.5 mg once daily.

|                       |           |
|-----------------------|-----------|
| Reporting group title | Stratum 1 |
|-----------------------|-----------|

Reporting group description:

Adults and children with neurofibromatosis type 1 (NF1) and inoperable plexiform neurofibromas (PN) with the potential to cause significant morbidity with documented progressive PN prior to study entry were enrolled in this stratum. Enrolled patients received everolimus (RAD001) in an open label manner. Recommended starting dose of everolimus depend on body surface area, starting from 2.5 mg once daily to 7.5 mg once daily.

| Serious adverse events                            | Stratum 2     | Stratum 1      |  |
|---|---------------|----------------|--|
| Total subjects affected by serious adverse events |               |                |  |
| subjects affected / exposed                       | 0 / 5 (0.00%) | 1 / 4 (25.00%) |  |
| number of deaths (all causes)                     | 0             | 0              |  |
| number of deaths resulting from adverse events    | 0             | 0              |  |
| Immune system disorders                           |               |                |  |
| Hypersensitivity                                  |               |                |  |
| subjects affected / exposed                       | 0 / 5 (0.00%) | 1 / 4 (25.00%) |  |
| occurrences causally related to treatment / all   | 0 / 0         | 0 / 1          |  |
| deaths causally related to treatment / all        | 0 / 0         | 0 / 0          |  |

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

| Non-serious adverse events                            | Stratum 2       | Stratum 1       |  |
|---|-----------------|-----------------|--|
| Total subjects affected by non-serious adverse events |                 |                 |  |
| subjects affected / exposed                           | 5 / 5 (100.00%) | 4 / 4 (100.00%) |  |

|  |   |   |  |
|--|---|---|--|
| Neoplasms benign, malignant and unspecified (incl cysts and polyps)<br>Fibroma<br>subjects affected / exposed<br>occurrences (all)   | 0 / 5 (0.00%)<br>0  | 1 / 4 (25.00%)<br>1   |  |
| Surgical and medical procedures<br>Cytoreductive surgery<br>subjects affected / exposed<br>occurrences (all)<br><br>Tooth extraction<br>subjects affected / exposed<br>occurrences (all)   | 1 / 5 (20.00%)<br>1<br><br>1 / 5 (20.00%)<br>2  | 0 / 4 (0.00%)<br>0<br><br>0 / 4 (0.00%)<br>0  |  |
| General disorders and administration site conditions<br>Asthenia<br>subjects affected / exposed<br>occurrences (all)<br><br>Chest pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Discomfort<br>subjects affected / exposed<br>occurrences (all)<br><br>Fatigue<br>subjects affected / exposed<br>occurrences (all)<br><br>Influenza like illness<br>subjects affected / exposed<br>occurrences (all)<br><br>Mucosal inflammation<br>subjects affected / exposed<br>occurrences (all)<br><br>Oedema peripheral<br>subjects affected / exposed<br>occurrences (all)<br><br>Pain<br>subjects affected / exposed<br>occurrences (all) | 1 / 5 (20.00%)<br>1<br><br>0 / 5 (0.00%)<br>0<br><br>0 / 5 (0.00%)<br>0<br><br>2 / 5 (40.00%)<br>2<br><br>1 / 5 (20.00%)<br>1<br><br>2 / 5 (40.00%)<br>3<br><br>0 / 5 (0.00%)<br>0<br><br>1 / 5 (20.00%)<br>1 | 0 / 4 (0.00%)<br>0<br><br>1 / 4 (25.00%)<br>1<br><br>1 / 4 (25.00%)<br>1<br><br>2 / 4 (50.00%)<br>2<br><br>3 / 4 (75.00%)<br>8<br><br>2 / 4 (50.00%)<br>3<br><br>1 / 4 (25.00%)<br>1<br><br>1 / 4 (25.00%)<br>1 |  |

|   |  |   |  |
|---|--|---|--|
| Peripheral swelling<br>subjects affected / exposed<br>occurrences (all)   | 0 / 5 (0.00%)<br>0   | 1 / 4 (25.00%)<br>2   |  |
| Reproductive system and breast disorders<br>Breast mass<br>subjects affected / exposed<br>occurrences (all)<br><br>Metrorrhagia<br>subjects affected / exposed<br>occurrences (all)<br><br>Vaginal haemorrhage<br>subjects affected / exposed<br>occurrences (all)  | 0 / 5 (0.00%)<br>0<br><br>0 / 5 (0.00%)<br>0<br><br>0 / 5 (0.00%)<br>0                             | 1 / 4 (25.00%)<br>1<br><br>1 / 4 (25.00%)<br>1<br><br>1 / 4 (25.00%)<br>1                           |  |
| Respiratory, thoracic and mediastinal disorders<br>Dysphonia<br>subjects affected / exposed<br>occurrences (all)<br><br>Dyspnoea<br>subjects affected / exposed<br>occurrences (all)<br><br>Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Pharyngeal erythema<br>subjects affected / exposed<br>occurrences (all) | 1 / 5 (20.00%)<br>1<br><br>0 / 5 (0.00%)<br>0<br><br>2 / 5 (40.00%)<br>2<br><br>0 / 5 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0<br><br>1 / 4 (25.00%)<br>1<br><br>1 / 4 (25.00%)<br>1<br><br>1 / 4 (25.00%)<br>1 |  |
| Psychiatric disorders<br>Anxiety<br>subjects affected / exposed<br>occurrences (all)<br><br>Insomnia<br>subjects affected / exposed<br>occurrences (all)<br><br>Sleep disorder<br>subjects affected / exposed<br>occurrences (all)  | 1 / 5 (20.00%)<br>1<br><br>1 / 5 (20.00%)<br>1<br><br>1 / 5 (20.00%)<br>1                          | 0 / 4 (0.00%)<br>0<br><br>0 / 4 (0.00%)<br>0<br><br>0 / 4 (0.00%)<br>0                              |  |

|  |                     |                     |  |
|--|---------------------|---------------------|--|
| Tic<br>subjects affected / exposed<br>occurrences (all)                                    | 0 / 5 (0.00%)<br>0  | 1 / 4 (25.00%)<br>1 |  |
| Investigations   |                     |                     |  |
| Blood cholesterol increased<br>subjects affected / exposed<br>occurrences (all)            | 2 / 5 (40.00%)<br>2 | 1 / 4 (25.00%)<br>2 |  |
| Blood creatine phosphokinase increased<br>subjects affected / exposed<br>occurrences (all) | 1 / 5 (20.00%)<br>3 | 0 / 4 (0.00%)<br>0  |  |
| Blood triglycerides increased<br>subjects affected / exposed<br>occurrences (all)          | 1 / 5 (20.00%)<br>1 | 1 / 4 (25.00%)<br>1 |  |
| Drug level increased<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 5 (0.00%)<br>0  | 1 / 4 (25.00%)<br>1 |  |
| Eosinophil count increased<br>subjects affected / exposed<br>occurrences (all)             | 1 / 5 (20.00%)<br>1 | 0 / 4 (0.00%)<br>0  |  |
| Low density lipoprotein increased<br>subjects affected / exposed<br>occurrences (all)      | 0 / 5 (0.00%)<br>0  | 1 / 4 (25.00%)<br>2 |  |
| Lymphocyte count decreased<br>subjects affected / exposed<br>occurrences (all)             | 0 / 5 (0.00%)<br>0  | 1 / 4 (25.00%)<br>2 |  |
| Platelet count decreased<br>subjects affected / exposed<br>occurrences (all)               | 1 / 5 (20.00%)<br>4 | 1 / 4 (25.00%)<br>1 |  |
| Injury, poisoning and procedural complications   |                     |                     |  |
| Tendonitis<br>subjects affected / exposed<br>occurrences (all)                             | 0 / 5 (0.00%)<br>0  | 1 / 4 (25.00%)<br>1 |  |
| Nervous system disorders   |                     |                     |  |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)                              | 1 / 5 (20.00%)<br>1 | 1 / 4 (25.00%)<br>1 |  |

|  |                     |                     |  |
|--|---------------------|---------------------|--|
| Headache<br>subjects affected / exposed<br>occurrences (all)                                     | 4 / 5 (80.00%)<br>4 | 3 / 4 (75.00%)<br>3 |  |
| Paraesthesia<br>subjects affected / exposed<br>occurrences (all)                                 | 0 / 5 (0.00%)<br>0  | 1 / 4 (25.00%)<br>1 |  |
| Ear and labyrinth disorders<br>Ear pain<br>subjects affected / exposed<br>occurrences (all)      | 0 / 5 (0.00%)<br>0  | 2 / 4 (50.00%)<br>2 |  |
| External ear inflammation<br>subjects affected / exposed<br>occurrences (all)                    | 1 / 5 (20.00%)<br>1 | 0 / 4 (0.00%)<br>0  |  |
| Eye disorders<br>Ocular hyperaemia<br>subjects affected / exposed<br>occurrences (all)           | 0 / 5 (0.00%)<br>0  | 1 / 4 (25.00%)<br>1 |  |
| Gastrointestinal disorders<br>Abdominal pain<br>subjects affected / exposed<br>occurrences (all) | 2 / 5 (40.00%)<br>2 | 1 / 4 (25.00%)<br>1 |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                                    | 0 / 5 (0.00%)<br>0  | 2 / 4 (50.00%)<br>3 |  |
| Dysphagia<br>subjects affected / exposed<br>occurrences (all)                                    | 0 / 5 (0.00%)<br>0  | 2 / 4 (50.00%)<br>2 |  |
| Flatulence<br>subjects affected / exposed<br>occurrences (all)                                   | 1 / 5 (20.00%)<br>1 | 0 / 4 (0.00%)<br>0  |  |
| Mouth ulceration<br>subjects affected / exposed<br>occurrences (all)                             | 1 / 5 (20.00%)<br>5 | 0 / 4 (0.00%)<br>0  |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)                                       | 0 / 5 (0.00%)<br>0  | 1 / 4 (25.00%)<br>1 |  |
| Stomatitis   |                     |                     |  |

|  |                     |                     |  |
|--|---------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all)                               | 1 / 5 (20.00%)<br>4 | 0 / 4 (0.00%)<br>0  |  |
| Toothache<br>subjects affected / exposed<br>occurrences (all)                  | 1 / 5 (20.00%)<br>1 | 1 / 4 (25.00%)<br>1 |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 5 (20.00%)<br>1 | 1 / 4 (25.00%)<br>1 |  |
| Skin and subcutaneous tissue disorders   |                     |                     |  |
| Alopecia<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 5 (20.00%)<br>1 | 0 / 4 (0.00%)<br>0  |  |
| Dermatitis acneiform<br>subjects affected / exposed<br>occurrences (all)       | 1 / 5 (20.00%)<br>1 | 0 / 4 (0.00%)<br>0  |  |
| Rash<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 5 (0.00%)<br>0  | 2 / 4 (50.00%)<br>2 |  |
| Musculoskeletal and connective tissue disorders                                |                     |                     |  |
| Musculoskeletal chest pain<br>subjects affected / exposed<br>occurrences (all) | 0 / 5 (0.00%)<br>0  | 1 / 4 (25.00%)<br>1 |  |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)          | 0 / 5 (0.00%)<br>0  | 2 / 4 (50.00%)<br>5 |  |
| Infections and infestations  |                     |                     |  |
| Eye infection<br>subjects affected / exposed<br>occurrences (all)              | 1 / 5 (20.00%)<br>1 | 0 / 4 (0.00%)<br>0  |  |
| Pneumonia<br>subjects affected / exposed<br>occurrences (all)                  | 1 / 5 (20.00%)<br>1 | 0 / 4 (0.00%)<br>0  |  |
| Skin infection<br>subjects affected / exposed<br>occurrences (all)             | 1 / 5 (20.00%)<br>1 | 0 / 4 (0.00%)<br>0  |  |
| Metabolism and nutrition disorders   |                     |                     |  |



|                             |                |                |  |
|-----------------------------|----------------|----------------|--|
| Decreased appetite          |                |                |  |
| subjects affected / exposed | 1 / 5 (20.00%) | 1 / 4 (25.00%) |  |
| occurrences (all)           | 1              | 1              |  |
| Hypertriglyceridaemia       |                |                |  |
| subjects affected / exposed | 1 / 5 (20.00%) | 1 / 4 (25.00%) |  |
| occurrences (all)           | 1              | 1              |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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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.

Study got terminated because of poor patient's accrual.

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.n>

Notes: