



## 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
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### 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
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<b>Arm title</b>	Stratum 1
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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
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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>
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#### 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>
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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
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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>
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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
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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
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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
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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
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### Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

### Reporting groups

Reporting group title	Stratum 2
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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
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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) Fibroma subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 4 (25.00%) 1	
Surgical and medical procedures Cytoreductive surgery subjects affected / exposed occurrences (all)  Tooth extraction subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1  1 / 5 (20.00%) 2	0 / 4 (0.00%) 0  0 / 4 (0.00%) 0	
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all)  Chest pain subjects affected / exposed occurrences (all)  Discomfort subjects affected / exposed occurrences (all)  Fatigue subjects affected / exposed occurrences (all)  Influenza like illness subjects affected / exposed occurrences (all)  Mucosal inflammation subjects affected / exposed occurrences (all)  Oedema peripheral subjects affected / exposed occurrences (all)  Pain subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1  0 / 5 (0.00%) 0  0 / 5 (0.00%) 0  2 / 5 (40.00%) 2  1 / 5 (20.00%) 1  2 / 5 (40.00%) 3  0 / 5 (0.00%) 0  1 / 5 (20.00%) 1	0 / 4 (0.00%) 0  1 / 4 (25.00%) 1  1 / 4 (25.00%) 1  2 / 4 (50.00%) 2  3 / 4 (75.00%) 8  2 / 4 (50.00%) 3  1 / 4 (25.00%) 1  1 / 4 (25.00%) 1	

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

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

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

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