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
Arm title	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 wereenrolled 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

Arm title	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

Number of subjects in period 1	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 wereenrolled 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 wereenrolled 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)[1][2]

End point description:

This endpoint was planned to be analyzed for only Stratum 1 patients. Progression of disease defined as a ≥ 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)[3][4]

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 ≥ 28days and no appearance of new lesions. - Partial response (PR): A ≥ 20% reduction in the sum of the volume of all index PN lesions for ≥ 28days. - Stable disease (SD): A ‹ 20% increase and ‹ 20% decrease in the sum of the volume of all index PN lesions for ≥ 28days.

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[5]

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[6]	0[7]		
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[8]	0[9]		
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 wereenrolled 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	0 / 5 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Surgical and medical procedures			
Cytoreductive surgery			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Tooth extraction			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Chest pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Discomfort			
subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	2 / 5 (40.00%)	2 / 4 (50.00%)	
occurrences (all)	2	2	
Influenza like illness			
subjects affected / exposed	1 / 5 (20.00%)	3 / 4 (75.00%)	
occurrences (all)	1	8	
Mucosal inflammation			
subjects affected / exposed	2 / 5 (40.00%)	2 / 4 (50.00%)	
occurrences (all)	3	3	
Oedema peripheral			
subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Pain			
subjects affected / exposed	1 / 5 (20.00%)	1 / 4 (25.00%)	
occurrences (all)	1	1	

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

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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: