Clinical trial results:
An open-label, multi-center, expanded access study of RAD001 in patients with angiomyolipoma associated with tuberous sclerosis complex (TSC)

Summary

EudraCT number	2012-005397-63
Trial protocol	ES
Global end of trial date	29 September 2014

Results information

Result version number	v1 (current)
This version publication date	14 June 2020
First version publication date	14 June 2020

Trial information

Trial identification

Sponsor protocol code	CRAD001MES12

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Novartis Farmacéutica, S.A
Sponsor organisation address	Gran Vía de les Corts Catalanes, 764, Barcelona, Spain, 08013
Public contact	Departamento Médico de Oncología, Novartis Farmacéutica, S.A, 00 34900353036, eecc.novartis@novartis.com
Scientific contact	Departamento Médico de Oncología, Novartis Farmacéutica, S.A, 00 34900353036, eecc.novartis@novartis.com

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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 September 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 September 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the dose-limiting safety of everolimus in subjects with angiomyolipoma associated with TSC.

Protection of trial subjects:

This study was conducted in compliance with Good Clinical Practice (GCP), including the archiving of essential documents.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 May 2013
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	Spain: 19
Worldwide total number of subjects	19
EEA total number of subjects	19

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	19
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled at 15 study centres in Spain.

Pre-assignment

Screening details:

Subjects enrolled in this study were diagnosed with angiomyolipoma (AML) associated with TSC.

Period 1

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

Arms

Arm title	Everolimus

Arm description:

Everolimus was administered following an oral daily continuous regimen of two 5 milligram (mg) tablets (10 mg, total daily dose) once a day at the same time everyday, either always with food or without food.

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:

The study drug was administered at a daily dose of two 5 mg tablets (10 mg, total daily dose) once a day.

Number of subjects in period 1	Everolimus
Started	19
Completed	19

Baseline characteristics

Reporting groups	
Reporting group title	Everolimus
Reporting group description:	
Everolimus was administered following an oral daily continuous regimen of two 5 milligram (mg) tablets (10 mg, total daily dose) once a day at the same time everyday, either always with food or without food.	

Reporting group values	Everolimus	Total	
Number of subjects	19	19	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	19	19	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
median	38		
full range (min-max)	20 to 62	-	
Gender categorical Units: Subjects			
Female	13	13	
Male	6	6	
Race Units: Subjects			
Caucasian	19	19	

End points

End points reporting groups

Reporting group title	Everolimus

Reporting group description:

Everolimus was administered following an oral daily continuous regimen of two 5 milligram (mg) tablets (10 mg, total daily dose) once a day at the same time everyday, either always with food or without food.

Primary: Number of Subjects With Dose-limiting Safety of Everolimus

End point title	Number of Subjects With Dose-limiting Safety of Everolimus[1]

End point description:

Safety population included all subjects who received at least one dose of study drug and had at least one post-baseline safety assessment.

End point type	Primary

End point timeframe:

Up to approximately 16 months

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 primary outcome measure

End point values	Everolimus			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: subjects				
Dose reduction	3			
Temporary interruption	3			
Dose reduction and Temporary interruption	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Response rate : Percentage of Subjects With Response of Angiomyolipoma to Everolimus

End point title	Response rate : Percentage of Subjects With Response of Angiomyolipoma to Everolimus

End point description:

Tumour response was assessed radiologically using magnetic resonance imaging (MRI) or computerised axial tomography (CT) scans. Tumour evaluations were recommended to be performed for all subjects, a renal MRI/CT scan on weeks 12, 24 and 48 following the start of treatment (with a ± 7 window), then every year unless the observation of angiomyolipoma response required a confirmation of a second scan approximately 12 weeks after (and not prior to 8 weeks after), and at the time of the study drug withdrawal. The AML radiological response was assessed following the predefined response criteria. Full Analysis Set included all subjects who received at least one dose of everolimus.

End point type	Secondary

End point timeframe:

Until disease progression, unacceptable toxicity, death, discontinuation from the study or until drug becomes commercially available in Spain or until 20 May 2014

End point values	Everolimus			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: percentage of subjects				
number (not applicable)	47.37			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Adverse Events and Serious Adverse Events

End point title	Number of Subjects With Adverse Events and Serious Adverse Events

End point description:

Safety population included all subjects who received at least one dose of RAD001 and had at least one post-baseline safety assessment.

End point type	Secondary

End point timeframe:

Up to approximately 16 months

End point values	Everolimus			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: subjects				
Adverse events	19			
Serious adverse events	1			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from first dose of study treatment until 28 days following the last dose of study treatment.

Adverse event reporting additional description:

Any sign or symptom that occurs during study treatment plus the 28 days post-treatment

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Everolimus

Reporting group description:

Everolimus was administered following an oral daily continuous regimen of two 5 milligram (mg) tablets (10 mg, total daily dose) once a day at the same time everyday, either always with food or without food.

Serious adverse events	Everolimus		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 19 (5.26%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Respiratory, thoracic and mediastinal disorders			
Pneumonia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Everolimus		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 19 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Ovarian cyst			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		

Vascular disorders Hypertension subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all)	 6 / 19 (31.58%) 6 1 / 19 (5.26%) 2		
Surgical and medical procedures Polypectomy subjects affected / exposed occurrences (all)	 1 / 19 (5.26%) 1		
General disorders and administration site conditions Mucosal inflammation subjects affected / exposed occurrences (all) Asthenia subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all) Mucosal dryness subjects affected / exposed occurrences (all)	 4 / 19 (21.05%) 7 2 / 19 (10.53%) 3 1 / 19 (5.26%) 2 1 / 19 (5.26%) 1		
Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all)	 1 / 19 (5.26%) 1		
Reproductive system and breast disorders Amenorrhoea subjects affected / exposed occurrences (all) Menstrual disorder subjects affected / exposed occurrences (all) Menorrhagia	 3 / 19 (15.79%) 3 1 / 19 (5.26%) 3		

subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Dysmenorrhoea			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Catarrh			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	4		
Pharyngitis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	3		
Nasopharyngitis			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	3		
Cough			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	3		
Epistaxis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	2		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	4 / 19 (21.05%)		
occurrences (all)	5		
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	2		
Transaminases increased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	2		
Alanine aminotransferase increased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Blood cholesterol increased			

subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	3		
Sciatica			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Microcytosis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Eye disorders			
Conjunctivitis			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Chalazion			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Eyelid oedema			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Gastrointestinal disorders			
Aphthous ulcer			
subjects affected / exposed	7 / 19 (36.84%)		
occurrences (all)	11		
Diarrhoea			
subjects affected / exposed	4 / 19 (21.05%)		
occurrences (all)	4		
Dysgeusia			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	3		
Abdominal pain upper			

subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Vomiting			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Gingival abscess			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Dry mouth			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Gastrointestinal pain			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Stomatitis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Gingival bleeding			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Odynophagia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			

subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	5		
Dermatitis			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Erythema			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Rash			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Alopecia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Rash maculo-papular			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Renal and urinary disorders			
Polyuria			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Proteinuria			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Myalgia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	2		
Arthralgia			

subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Neck pain			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Muscle spasms			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	8		
Oral herpes			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	2		
Gingivitis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Herpes zoster			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Ear lobe infection			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Respiratory tract infection			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	9 / 19 (47.37%)		
occurrences (all)	11		
Hypertriglyceridaemia			
subjects affected / exposed	5 / 19 (26.32%)		
occurrences (all)	8		
Decreased appetite			

subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 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

None reported