Clinical trial results:
A randomized, open label, two-way crossover study investigating the relative bioavailability of a single 5 mg dose of everolimus administered as either 5x1 mg everolimus intact tablets or 5x1 mg everolimus tablets suspended in 30 mL of water to healthy subjects.

Summary

EudraCT number	2012-000299-40
Trial protocol	Outside EU/EEA
Global end of trial date	12 January 2009

Results information

Result version number	v1 (current)
This version publication date	25 October 2018
First version publication date	25 October 2018

Trial information

Trial identification

Sponsor protocol code	CRAD001C2121

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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 61324 1111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, +41 61324 1111,

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	12 January 2009
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 January 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to evaluate the bioavailability of 5*1 milligrams (mg) everolimus intact tablets and tablets suspended in 30 millilitres (mL) of water.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 November 2008
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	United States: 40
Worldwide total number of subjects	40
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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	40
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at one center in the United States.

Pre-assignment

Screening details:

A total of 40 subjects were enrolled, of which 37 completed the study.

Period 1

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

Blinding implementation details:

The study was open label study, hence no blinding was performed.

Arms

Are arms mutually exclusive?	Yes
Arm title	Everolimus (Intact then Suspended)

Arm description:

Subjects after (30 minutes) having a light, fat-free breakfast were orally administered with dose of 5 mg everolimus intact tablets (reference product) followed by dose of 5 mg everolimus suspended tablets in 30 mL with additional 30 mL of water after suspension (test product) on Day 1 and 15, respectively. A washout of 14 days was maintained between the treatment period.

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

Dosage and administration details:

Subjects were orally administered with 5 mg everolimus intact tablet (5 tablets- 1 mg each) followed by 5 mg everolimus suspended tablets (5 tablets- 1 mg each) in 30 mL with additional 30 mL of water after suspension on Day 1 and 15, respectively.

Arm title	Everolimus (Suspended then Intact)

Arm description:

Subjects after (30 minutes) having a light, fat-free breakfast were orally administered with dose of 5 mg everolimus suspended tablets in 30 mL with additional 30 mL of water after suspension (test product) followed by dose of 5 mg everolimus intact tablets (reference product) on Day 1 and 15, respectively. A washout of 14 days was maintained between the treatment period.

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

Dosage and administration details:

Subjects were orally administered with 5 mg everolimus suspended tablets (5 tablets- 1 mg each) in 30 mL with additional 30 mL of water after suspension followed by 5 mg everolimus intact tablet (5 tablets- 1 mg each) on Day 1 and 15, respectively.

Number of subjects in period 1	Everolimus (Intact then Suspended)	Everolimus (Suspended then Intact)
Started	20	20
Completed	17	20
Not completed	3	0
Abnormal laboratory values	2	-
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Everolimus (Intact then Suspended)
Reporting group description:	
Subjects after (30 minutes) having a light, fat-free breakfast were orally administered with dose of 5 mg everolimus intact tablets (reference product) followed by dose of 5 mg everolimus suspended tablets in 30 mL with additional 30 mL of water after suspension (test product) on Day 1 and 15, respectively. A washout of 14 days was maintained between the treatment period.	
Reporting group title	Everolimus (Suspended then Intact)
Reporting group description:	
Subjects after (30 minutes) having a light, fat-free breakfast were orally administered with dose of 5 mg everolimus suspended tablets in 30 mL with additional 30 mL of water after suspension (test product) followed by dose of 5 mg everolimus intact tablets (reference product) on Day 1 and 15, respectively. A washout of 14 days was maintained between the treatment period.	

Reporting group values	Everolimus (Intact then Suspended)	Everolimus (Suspended then Intact)	Total
Number of subjects	20	20	40
Age categorical Units: Subjects			
Adults (18-64 years)	20	20	40
Age continuous Units: years			
arithmetic mean	34.2	32.1	
standard deviation	± 9.22	± 6.58	-
Gender categorical Units: Subjects			
Female	19	18	37
Male	1	2	3

End points

End points reporting groups

Reporting group title	Everolimus (Intact then Suspended)

Reporting group description:

Subjects after (30 minutes) having a light, fat-free breakfast were orally administered with dose of 5 mg everolimus intact tablets (reference product) followed by dose of 5 mg everolimus suspended tablets in 30 mL with additional 30 mL of water after suspension (test product) on Day 1 and 15, respectively. A washout of 14 days was maintained between the treatment period.

Reporting group title	Everolimus (Suspended then Intact)

Reporting group description:

Subjects after (30 minutes) having a light, fat-free breakfast were orally administered with dose of 5 mg everolimus suspended tablets in 30 mL with additional 30 mL of water after suspension (test product) followed by dose of 5 mg everolimus intact tablets (reference product) on Day 1 and 15, respectively. A washout of 14 days was maintained between the treatment period.

Subject analysis set title	Everolimus (Intact)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All subjects who received 5 mg everolimus intact tablets during the study.

Subject analysis set title	Everolimus (Suspended)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All subjects who received 5 mg everolimus suspended tablets in 30 mL of water during the study.

Primary: Area under the curve (AUC) from time zero to infinity (AUC0-inf) of everolimus

End point title	Area under the curve (AUC) from time zero to infinity (AUC0-inf) of everolimus

End point description:

(AUC0-inf) was defined as the area under the curve from time zero to infinity. AUC0-inf was estimated by non-compartmental method, using WinNonLin version 5.0.1. Everolimus concentrations in blood were determined by Liquid chromatography–mass spectrometry (LC-MS) method following liquid extraction. The method had a lower limit of quantification (LLOQ) of 0.3 ng/mL. The analysis was performed in pharmacokinetic analysis set (PAS) population, defined as all subjects who had completed at least one period with evaluable pharmacokinetic samples.

End point type	Primary

End point timeframe:

Pre dose, 0.5 h, 1 h, 1.5 h, 2 h, 2.5 h, 3 h, 4 h, 5 h, 6 h, 8 h, 12 h, 24 h at Day 1, 12 h and 24 h at Day 2, Day 3, Day 4, Day 5 and Day 6

End point values	Everolimus (Intact)	Everolimus (Suspended)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	39	36		
Units: Nanograms (ng)*hour(h) / Milliliter(mL)				
geometric mean (geometric coefficient of variation)	192.32 (± 38.89)	169.54 (± 43.87)		

Statistical analyses

Statistical analysis title	AUC0-inf of everolimus

Statistical analysis description:

Comparison of AUC0-inf for everolimus intact and suspended was evaluated. AUC0-inf was analyzed using a linear mixed model. The number of subjects analyzed for this end point were 39 for everolimus (intact) and 36 for everolimus (suspended), but since this is a cross-over study, the subjects analyzed feature as 75 below, which is the total of the two arms that are being compared [everolimus (intact) (N=39) and everolimus (suspended) (N=36)].

Comparison groups	Everolimus (Intact) v Everolimus (Suspended)
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Geometric mean ratio
Point estimate	0.88
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.8
upper limit	0.96

Primary: Maximum drug concentration in blood (Cmax) of everolimus

End point title	Maximum drug concentration in blood (Cmax) of everolimus

End point description:

Cmax was defined as the maximum (peak) drug concentration in blood after drug administration. It was estimated by means of non-compartmental method, using WinNonLin v5.0.1. Everolimus concentrations in blood were determined by a LC-MS method following liquid extraction. The method had a LLOQ of 0.3 ng/mL. The analysis was performed in PAS population.

End point type	Primary

End point timeframe:

Pre dose, 0.5 h, 1 h, 1.5 h, 2 h, 2.5 h, 3 h, 4 h, 5 h, 6 h, 8 h, 12 h, 24 h at Day 1, 12 h and 24 h at Day 2, Day 3, Day 4, Day 5 and Day 6

End point values	Everolimus (Intact)	Everolimus (Suspended)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	39	36		
Units: ng/mL				
geometric mean (geometric coefficient of variation)	26.52 (± 44.34)	19.08 (± 43.58)		

Statistical analyses

Statistical analysis title	Cmax of everolimus

Statistical analysis description:

Comparison of Cmax for everolimus intact and suspended was evaluated. Cmax was analyzed using a linear mixed model. The number of subjects analyzed for this end point were 39 for everolimus (intact) and 36 for everolimus (suspended), but since this is a cross-over study, the subjects analyzed feature

as 75 below, which is the total of the two arms that are being compared [everolimus (intact) (N=39) and everolimus (suspended) (N=36)].

Comparison groups	Everolimus (Intact) v Everolimus (Suspended)
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Geometric mean ratio
Point estimate	0.72
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.63
upper limit	0.82

Secondary: Area under the curve (AUC) from time zero to time of the last quantifiable concentration in blood AUC(0-t) of everolimus

End point title	Area under the curve (AUC) from time zero to time of the last quantifiable concentration in blood AUC(0-t) of everolimus

End point description:

AUC(0-t) was defined as the AUC from time zero to time of the last quantifiable concentration in blood. AUC(0-t) was estimated by means of non-compartmental method, using WinNonLin v5.0.1. Everolimus concentrations in blood were determined by a LC-MS method following liquid extraction. The method had a LLOQ of 0.3 ng/mL. The analysis was performed in PAS population.

End point type	Secondary

End point timeframe:

Pre dose, 0.5 h, 1 h, 1.5 h, 2 h, 2.5 h, 3 h, 4 h, 5 h, 6 h, 8 h, 12 h, 24 h at Day 1, 12 h and 24 h at Day 2, Day 3, Day 4, Day 5 and Day 6

End point values	Everolimus (Intact)	Everolimus (Suspended)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	39	36		
Units: ng*h/mL				
geometric mean (geometric coefficient of variation)	170.76 (± 42.76)	146.71 (± 49.21)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to reach peak or maximum concentration in blood (Tmax) of everolimus

End point title	Time to reach peak or maximum concentration in blood (Tmax) of everolimus

End point description:

Tmax was defined as the time to reach peak or maximum concentration in blood. Tmax was estimated by means of non-compartmental method, using WinNonLin v5.0.1. Everolimus concentrations in blood

were determined by a LC-MS method following liquid extraction. The method had a LLOQ of 0.3 ng/mL. The analysis was performed in PAS population.

End point type	Secondary

End point timeframe:

Pre dose, 0.5 h, 1 h, 1.5 h, 2 h, 2.5 h, 3 h, 4 h, 5 h, 6 h, 8 h, 12 h, 24 h at Day 1, 12 h and 24 h at Day 2, Day 3, Day 4, Day 5 and Day 6

End point values	Everolimus (Intact)	Everolimus (Suspended)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	39	36		
Units: hour				
median (full range (min-max))	1 (0.5 to 1.5)	1 (0.5 to 2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Slowest disposition (hybrid) rate constant (λZ) of everolimus

End point title	Slowest disposition (hybrid) rate constant (λZ) of everolimus

End point description:

λZ was defined as the slowest disposition (hybrid) rate constant. λZ was estimated by means of non-compartmental method, using WinNonLin v5.0.1. Everolimus concentrations in blood were determined by a LC-MS method following liquid extraction. The method had a LLOQ of 0.3 ng/mL. The analysis was performed in PAS population.

End point type	Secondary

End point timeframe:

Pre dose, 0.5 h, 1 h, 1.5 h, 2 h, 2.5 h, 3 h, 4 h, 5 h, 6 h, 8 h, 12 h, 24 h at Day 1, 12 h and 24 h at Day 2, Day 3, Day 4, Day 5 and Day 6

End point values	Everolimus (Intact)	Everolimus (Suspended)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	39	36		
Units: per hour (1/h)				
geometric mean (geometric coefficient of variation)	0.02 (± 22.75)	0.02 (± 21.54)		

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent volume of distribution (Vd/F) of everolimus

End point title	Apparent volume of distribution (Vd/F) of everolimus

End point description:

Vd/F was defined as the apparent volume of distribution. Vd/F was estimated by means of non-compartmental method, using WinNonLin v5.0.1. Everolimus concentrations in blood were determined by a LC-MS method following liquid extraction. The method had a LLOQ of 0.3 ng/mL. The analysis was performed in PAS population.

End point type	Secondary

End point timeframe:

Pre dose, 0.5 h, 1 h, 1.5 h, 2 h, 2.5 h, 3 h, 4 h, 5 h, 6 h, 8 h, 12 h, 24 h at Day 1, 12 h and 24 h at Day 2, Day 3, Day 4, Day 5 and Day 6

End point values	Everolimus (Intact)	Everolimus (Suspended)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	39	36		
Units: litre(s)				
geometric mean (geometric coefficient of variation)	1317.92 (± 35.23)	1494.39 (± 40.43)		

Statistical analyses

No statistical analyses for this end point

Secondary: Total body apparent oral clearance of drug (CL/F) from the blood of everolimus

End point title	Total body apparent oral clearance of drug (CL/F) from the blood of everolimus

End point description:

CL/F was defined as the total body apparent oral clearance of drug. CL/F was estimated by means of non-compartmental method, using WinNonLin v5.0.1. Everolimus concentrations in blood were determined by a LC-MS method following liquid extraction. The method had a LLOQ of 0.3 ng/mL. The analysis was performed in PAS population.

End point type	Secondary

End point timeframe:

Pre dose, 0.5 h, 1 h, 1.5 h, 2 h, 2.5 h, 3 h, 4 h, 5 h, 6 h, 8 h, 12 h, 24 h at Day 1, 12 h and 24 h at Day 2, Day 3, Day 4, Day 5 and Day 6

End point values	Everolimus (Intact)	Everolimus (Suspended)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	39	36		
Units: Litre (L)/hour(h)/meter square(m2)				
geometric mean (geometric coefficient of variation)	12.82 (± 46.65)	14.45 (± 48.86)		

Statistical analyses

No statistical analyses for this end point

Secondary: Elimination half-life associated with the terminal slope (λz) of a semi logarithmic concentration-time curve (T ½) of everolimus

End point title	Elimination half-life associated with the terminal slope (λz) of a semi logarithmic concentration-time curve (T ½) of everolimus

End point description:

T ½ was defined as the elimination half-life associated with the terminal slope (λz) of a semi logarithmic concentration-time curve. T ½ was estimated by means of non-compartmental method, using WinNonLin v5.0.1. Everolimus concentrations in blood were determined by a LC-MS method following liquid extraction. The method had a LLOQ of 0.3 ng/mL. The analysis was performed in PAS population.

End point type	Secondary

End point timeframe:

Pre dose, 0.5 h, 1 h, 1.5 h, 2 h, 2.5 h, 3 h, 4 h, 5 h, 6 h, 8 h, 12 h, 24 h at Day 1, 12 h and 24 h at Day 2, Day 3, Day 4, Day 5 and Day 6

End point values	Everolimus (Intact)	Everolimus (Suspended)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	39	36		
Units: hour				
median (full range (min-max))	35.85 (22.5 to 67.5)	34.934 (20.3 to 64.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with Adverse Events (AEs), Serious Adverse Events (SAEs), AE leading to discontinuation and who died

End point title	Number of subjects with Adverse Events (AEs), Serious Adverse Events (SAEs), AE leading to discontinuation and who died

End point description:

AEs are defined as any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease which either occurs during study, having been absent at baseline, or, if present at baseline, appears to worsen. Serious adverse events are any untoward medical occurrences that result in death, are life threatening, require (or prolong) hospitalization, cause persistent or significant disability/incapacity, result in congenital anomalies or birth defects, or are other conditions which in judgment of investigators represent significant hazards. The analysis was performed on safety set population defined as all subjects who received at least one of the study treatment.

End point type	Secondary

End point timeframe:

From day 1 to day 29

End point values	Everolimus (Intact)	Everolimus (Suspended)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	40	37		
Units: Subjects				
AEs	15	14		
SAEs	0	0		
Deaths	0	0		
AEs leading to discontinuation	2	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Serious Adverse Events are monitored from date of First Subject First Visit (FSFV) until Last Subject Last Visit (LSLV). All other adverse events are monitored from First Subject First Treatment until LSLV	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	11.1

Reporting groups	
Reporting group title	Everolimus (Intact)
Reporting group description:	
All subjects who received 5 mg everolimus intact tablets during the study.	
Reporting group title	All Subjects
Reporting group description:	
All subjects who received 5 mg everolimus intact tablets or suspended tablets in 30 mL of water during the study.	
Reporting group title	Everolimus (Suspended)
Reporting group description:	
All subjects who received 5 mg everolimus suspended tablets in 30 mL of water during the study.	

Serious adverse events	Everolimus (Intact)	All Subjects	Everolimus (Suspended)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 40 (0.00%)	0 / 40 (0.00%)	0 / 37 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	Everolimus (Intact)	All Subjects	Everolimus (Suspended)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 40 (32.50%)	20 / 40 (50.00%)	12 / 37 (32.43%)
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	2 / 40 (5.00%)	3 / 40 (7.50%)	2 / 37 (5.41%)
occurrences (all)	2	4	2
ASPARTATE AMINOTRANSFERASE INCREASED			

subjects affected / exposed	2 / 40 (5.00%)	3 / 40 (7.50%)	2 / 37 (5.41%)
occurrences (all)	2	4	2
BLOOD TRIGLYCERIDES INCREASED			
subjects affected / exposed	2 / 40 (5.00%)	2 / 40 (5.00%)	0 / 37 (0.00%)
occurrences (all)	2	2	0
NEUTROPHIL COUNT INCREASED			
subjects affected / exposed	1 / 40 (2.50%)	3 / 40 (7.50%)	2 / 37 (5.41%)
occurrences (all)	1	3	2
WHITE BLOOD CELL COUNT INCREASED			
subjects affected / exposed	1 / 40 (2.50%)	3 / 40 (7.50%)	2 / 37 (5.41%)
occurrences (all)	1	3	2
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	2 / 40 (5.00%)	2 / 40 (5.00%)	1 / 37 (2.70%)
occurrences (all)	2	3	1
HEADACHE			
subjects affected / exposed	6 / 40 (15.00%)	8 / 40 (20.00%)	2 / 37 (5.41%)
occurrences (all)	7	9	2
SOMNOLENCE			
subjects affected / exposed	1 / 40 (2.50%)	2 / 40 (5.00%)	1 / 37 (2.70%)
occurrences (all)	1	2	1
Gastrointestinal disorders			
DIARRHOEA			
subjects affected / exposed	1 / 40 (2.50%)	4 / 40 (10.00%)	3 / 37 (8.11%)
occurrences (all)	1	4	3
FLATULENCE			
subjects affected / exposed	2 / 40 (5.00%)	2 / 40 (5.00%)	1 / 37 (2.70%)
occurrences (all)	3	5	2
NAUSEA			
subjects affected / exposed	1 / 40 (2.50%)	2 / 40 (5.00%)	1 / 37 (2.70%)
occurrences (all)	1	2	1
VOMITING			
subjects affected / exposed	1 / 40 (2.50%)	2 / 40 (5.00%)	1 / 37 (2.70%)
occurrences (all)	1	2	1
Respiratory, thoracic and mediastinal disorders			

NASAL CONGESTION subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0	2 / 40 (5.00%) 2	2 / 37 (5.41%) 2
Skin and subcutaneous tissue disorders PRURITUS subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	2 / 40 (5.00%) 2	1 / 37 (2.70%) 1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 November 2008	The amendment excluded female subjects with child-bearing potential from the clinical study. All female subjects in the clinical study were to be either post-menopausal or surgically sterilized.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported