Clinical trial results:
An open label, single arm trial to evaluate patients with metastatic renal cell carcinoma (mRCC) treated with everolimus after failure of first line therapy with sunitinib or pazopanib
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	2011-003416-23
Trial protocol	DE
Global end of trial date	01 April 2016

Results information

Result version number	v1 (current)
This version publication date	15 July 2018
First version publication date	15 July 2018

Trial information

Trial identification

Sponsor protocol code	CRAD001LDE43

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01514448
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 April 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 April 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective was to estimate the rate of patients free of progression after 6 months of treatment start with everolimus after failure of first-line sunitinib or pazopanib therapy.

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	02 July 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	Germany: 29
Worldwide total number of subjects	29
EEA total number of subjects	29

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)	10
From 65 to 84 years	19
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Single arm study of everolimus broken down into 2 subgroups for analyses and safety based on failed 1st line therapy (sunitinib or pazopanib) prior to starting study.

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	1st line SUN

Arm description:

Patients that failed 1st line therapy Sunitinib (SUN) prior to starting study. Patients were on Everolimus 10 mg orally once daily until disease progression, occurrence of intolerable toxicity, start of another anticancer treatment or withdrawn consent.

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

Dosage and administration details:

Everolimus 10mg/day oral tablet for 28 days cycle

Arm title	1st line PAZ

Arm description:

Patients that failed 1st line therapy Pazopanib (PAZ) prior to starting study. Patients were on Everolimus 10 mg orally once daily until disease progression, occurrence of intolerable toxicity, start of another anticancer treatment or withdrawn consent.

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

Dosage and administration details:

Everolimus 10mg/day oral tablet for 28 days cycle

Number of subjects in period 1	1st line SUN	1st line PAZ
Started	16	13
Full Analysis Set (FAS)	12	13
Completed	4	5
Not completed	12	8
Consent withdrawn by subject	2	-
Death	7	8
New Cancer Therapy	1	-
Lost to follow-up	2	-

Baseline characteristics

Reporting groups	
Reporting group title	1st line SUN
Reporting group description:	
Patients that failed 1st line therapy Sunitinib (SUN) prior to starting study. Patients were on Everolimus 10 mg orally once daily until disease progression, occurrence of intolerable toxicity, start of another anticancer treatment or withdrawn consent.	
Reporting group title	1st line PAZ
Reporting group description:	
Patients that failed 1st line therapy Pazopanib (PAZ) prior to starting study. Patients were on Everolimus 10 mg orally once daily until disease progression, occurrence of intolerable toxicity, start of another anticancer treatment or withdrawn consent.	

Reporting group values	1st line SUN	1st line PAZ	Total
Number of subjects	16	13	29
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	7	3	10
From 65-84 years	9	10	19
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	67.5	71.3	
standard deviation	± 8.2	± 6	-
Gender, Male/Female Units: Subjects			
Female	7	2	9
Male	9	11	20

End points

End points reporting groups

Reporting group title	1st line SUN

Reporting group description:

Patients that failed 1st line therapy Sunitinib (SUN) prior to starting study. Patients were on Everolimus 10 mg orally once daily until disease progression, occurrence of intolerable toxicity, start of another anticancer treatment or withdrawn consent.

Reporting group title	1st line PAZ

Reporting group description:

Patients that failed 1st line therapy Pazopanib (PAZ) prior to starting study. Patients were on Everolimus 10 mg orally once daily until disease progression, occurrence of intolerable toxicity, start of another anticancer treatment or withdrawn consent.

Primary: Percentage of progression-free patients by month 6

End point title	Percentage of progression-free patients by month 6[1]

End point description:

Percentage of progression-free patients by month 6 after starting everolimus treatment. For the purpose of the binomial design of the study, a patient being 'progression-free' will be defined as a patient without disease progression by month 6 whereas a subject with progressive disease by month 6 will not be counted as 'progression-free'. The primary variable was derived from radiologic tumor assessments according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1.) "No statistical analysis was planned for this primary outcome."

End point type	Primary

End point timeframe:

Month 6

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

End point values	1st line SUN	1st line PAZ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	13		
Units: Percentage of participants				
number (not applicable)	8.3	46.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients with Overall Response Rate (ORR) treated with everolimus after failure of first-line sunitinib or pazopanib therapy at Month 6

End point title	Percentage of patients with Overall Response Rate (ORR) treated with everolimus after failure of first-line sunitinib or pazopanib therapy at Month 6

End point description:

Overall response rate (ORR) is the Percentage of patients with a best overall response of complete response (CR) or partial response (PR) by month 6. ORR was assessed according to RECIST 1.1 criteria.

End point type	Secondary

End point timeframe:

Month 6

End point values	1st line SUN	1st line PAZ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	13		
Units: percentage of participants				
number (not applicable)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) as the time interval between first intake of everolimus and first documented disease progression or death due to any cause

End point title	Progression-Free Survival (PFS) as the time interval between first intake of everolimus and first documented disease progression or death due to any cause

End point description:

Progression-free survival (PFS) is the time from date of start of treatment to the date of event defined as the first documented progression or death due to any cause. If a patient did not have an event, progression-free survival was censored at the date of last adequate tumor assessment

End point type	Secondary

End point timeframe:

24 months

End point values	1st line SUN	1st line PAZ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	13		
Units: months				
median (confidence interval 80%)	2.8 (2.6 to 3.1)	8 (3 to 10.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS) of patients treated with everolimus after failure of first-line sunitinib or pazopanib therapy up to 48 months

End point title	Overall survival (OS) of patients treated with everolimus after failure of first-line sunitinib or pazopanib therapy up to 48 months

End point description:

Overall survival (OS) was defined as the time from date of start of treatment to date of death due to any cause. If a patient was not known to have died, survival will be censored at the date of last contact.

End point type	Secondary

End point timeframe:

48 months

End point values	1st line SUN	1st line PAZ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	13		
Units: months				
median (confidence interval 80%)	14.8 (10 to 9999)	20.4 (13.6 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response (DOR) in patients treated with everolimus after failure of first-line sunitinib or pazopanib therapy up to 48 months

End point title	Duration of response (DOR) in patients treated with everolimus after failure of first-line sunitinib or pazopanib therapy up to 48 months

End point description:

The duration of overall response (DOR) was defined as the time from the first occurrence of a confirmed Complete Response (CR) or Partial Response (PR) (as per investigator assessment according to RECIST 1.1) until the date of the first documented disease progression or death due to underlying cancer. If a patient did not have an event or received any further anticancer therapy, duration of overall response was censored at the date of last adequate tumor assessment. Duration of response was displayed only for patients whose best overall response was CR or PR. As none of the patients showed any response (CR or PR), DOR could not be calculated

End point type	Secondary

End point timeframe:

48 months

End point values	1st line SUN	1st line PAZ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	13		
Units: months	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from the start of study drug until 28 days after last dose for each patient.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	EVE following 1st line SUN
Reporting group description:	
EVE following 1st line SUN	
Reporting group title	Everolimus
Reporting group description:	
Everolimus	
Reporting group title	EVE following 1st line PAZ
Reporting group description:	
EVE following 1st line PAZ	

Serious adverse events	EVE following 1st line SUN	Everolimus	EVE following 1st line PAZ
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 16 (37.50%)	14 / 29 (48.28%)	8 / 13 (61.54%)
number of deaths (all causes)	1	2	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
MALIGNANT NEOPLASM PROGRESSION			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Cardiac disorders			
ATRIOVENTRICULAR BLOCK COMPLETE			
subjects affected / exposed	0 / 16 (0.00%)	1 / 29 (3.45%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

PERICARDIAL EFFUSION			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
CEREBROVASCULAR ACCIDENT			
subjects affected / exposed	0 / 16 (0.00%)	1 / 29 (3.45%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEMENTIA			
subjects affected / exposed	0 / 16 (0.00%)	1 / 29 (3.45%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SYNCOPE			
subjects affected / exposed	0 / 16 (0.00%)	1 / 29 (3.45%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	1 / 16 (6.25%)	2 / 29 (6.90%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	0 / 16 (0.00%)	1 / 29 (3.45%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	1 / 16 (6.25%)	2 / 29 (6.90%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 1	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYREXIA			

subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	0 / 16 (0.00%)	1 / 29 (3.45%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ENTEROCUTANEOUS FISTULA			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMORRHOIDS			
subjects affected / exposed	0 / 16 (0.00%)	1 / 29 (3.45%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NAUSEA			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
STOMATITIS			
subjects affected / exposed	0 / 16 (0.00%)	1 / 29 (3.45%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VOMITING			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
DYSPNOEA			
subjects affected / exposed	0 / 16 (0.00%)	2 / 29 (6.90%)	2 / 13 (15.38%)
occurrences causally related to treatment / all	0 / 0	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

HAEMOPTYSIS			
subjects affected / exposed	0 / 16 (0.00%)	1 / 29 (3.45%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PLEURAL EFFUSION			
subjects affected / exposed	1 / 16 (6.25%)	4 / 29 (13.79%)	3 / 13 (23.08%)
occurrences causally related to treatment / all	0 / 1	2 / 5	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONITIS			
subjects affected / exposed	0 / 16 (0.00%)	1 / 29 (3.45%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
POLYURIA			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RENAL FAILURE			
subjects affected / exposed	0 / 16 (0.00%)	1 / 29 (3.45%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
FLANK PAIN			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
ENDOCARDITIS			
subjects affected / exposed	1 / 16 (6.25%)	2 / 29 (6.90%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ABDOMINAL ABSCESS			

subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROINTESTINAL INFECTION			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA			
subjects affected / exposed	1 / 16 (6.25%)	2 / 29 (6.90%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
HYPOALBUMINAEMIA			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPONATRAEMIA			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	EVE following 1st line SUN	Everolimus	EVE following 1st line PAZ
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 16 (93.75%)	28 / 29 (96.55%)	13 / 13 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
TUMOUR PAIN			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
Vascular disorders			
DEEP VEIN THROMBOSIS			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	1	1	0

BLOOD PRESSURE FLUCTUATION			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
HYPERTENSION			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
PERIPHERAL COLDNESS			
subjects affected / exposed	0 / 16 (0.00%)	2 / 29 (6.90%)	2 / 13 (15.38%)
occurrences (all)	0	2	2
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
CHILLS			
subjects affected / exposed	0 / 16 (0.00%)	1 / 29 (3.45%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
FACE OEDEMA			
subjects affected / exposed	1 / 16 (6.25%)	2 / 29 (6.90%)	1 / 13 (7.69%)
occurrences (all)	2	3	1
FATIGUE			
subjects affected / exposed	5 / 16 (31.25%)	12 / 29 (41.38%)	7 / 13 (53.85%)
occurrences (all)	5	12	7
GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	1 / 16 (6.25%)	2 / 29 (6.90%)	1 / 13 (7.69%)
occurrences (all)	1	2	1
FEELING COLD			
subjects affected / exposed	0 / 16 (0.00%)	1 / 29 (3.45%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
OEDEMA PERIPHERAL			
subjects affected / exposed	2 / 16 (12.50%)	9 / 29 (31.03%)	7 / 13 (53.85%)
occurrences (all)	2	10	8
PYREXIA			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
Reproductive system and breast disorders			

GENITAL TRACT INFLAMMATION			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
PELVIC PAIN			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
Respiratory, thoracic and mediastinal disorders			
DYSPNOEA			
subjects affected / exposed	2 / 16 (12.50%)	7 / 29 (24.14%)	5 / 13 (38.46%)
occurrences (all)	2	8	6
COUGH			
subjects affected / exposed	6 / 16 (37.50%)	11 / 29 (37.93%)	5 / 13 (38.46%)
occurrences (all)	6	12	6
ALVEOLITIS			
subjects affected / exposed	0 / 16 (0.00%)	1 / 29 (3.45%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
EPISTAXIS			
subjects affected / exposed	2 / 16 (12.50%)	7 / 29 (24.14%)	5 / 13 (38.46%)
occurrences (all)	2	8	6
DYSPNOEA EXERTIONAL			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	2	2	0
DYSPNOEA AT REST			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
HYPOXIA			
subjects affected / exposed	0 / 16 (0.00%)	1 / 29 (3.45%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
NASAL INFLAMMATION			
subjects affected / exposed	0 / 16 (0.00%)	1 / 29 (3.45%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
PLEURAL EFFUSION			
subjects affected / exposed	0 / 16 (0.00%)	2 / 29 (6.90%)	2 / 13 (15.38%)
occurrences (all)	0	3	3
PAINFUL RESPIRATION			

subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
OROPHARYNGEAL PAIN			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
TACHYPNOEA			
subjects affected / exposed	1 / 16 (6.25%)	2 / 29 (6.90%)	1 / 13 (7.69%)
occurrences (all)	1	2	1
PULMONARY FIBROSIS			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
PNEUMONITIS			
subjects affected / exposed	1 / 16 (6.25%)	3 / 29 (10.34%)	2 / 13 (15.38%)
occurrences (all)	2	4	2
Psychiatric disorders			
APATHY			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
DEPRESSION			
subjects affected / exposed	0 / 16 (0.00%)	1 / 29 (3.45%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
RESTLESSNESS			
subjects affected / exposed	0 / 16 (0.00%)	1 / 29 (3.45%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
SLEEP DISORDER			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
BLOOD CHLORIDE INCREASED			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
BLOOD CHLORIDE DECREASED			

subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
BLOOD ALKALINE PHOSPHATASE INCREASED			
subjects affected / exposed	3 / 16 (18.75%)	3 / 29 (10.34%)	0 / 13 (0.00%)
occurrences (all)	3	3	0
BLOOD CREATININE INCREASED			
subjects affected / exposed	3 / 16 (18.75%)	5 / 29 (17.24%)	2 / 13 (15.38%)
occurrences (all)	3	5	2
BLOOD LACTATE DEHYDROGENASE INCREASED			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
BLOOD PHOSPHORUS DECREASED			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
CLOSTRIDIUM TEST POSITIVE			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
GAMMA-GLUTAMYLTRANSFERASE INCREASED			
subjects affected / exposed	3 / 16 (18.75%)	3 / 29 (10.34%)	0 / 13 (0.00%)
occurrences (all)	4	4	0
GLUCOSE URINE PRESENT			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
HAEMATOCRIT DECREASED			
subjects affected / exposed	3 / 16 (18.75%)	3 / 29 (10.34%)	0 / 13 (0.00%)
occurrences (all)	3	3	0
HIGH DENSITY LIPOPROTEIN DECREASED			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
LOW DENSITY LIPOPROTEIN INCREASED			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
RED BLOOD CELL COUNT DECREASED			

subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
PLATELET COUNT INCREASED			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
NEUTROPHIL COUNT INCREASED			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
WEIGHT DECREASED			
subjects affected / exposed	2 / 16 (12.50%)	3 / 29 (10.34%)	1 / 13 (7.69%)
occurrences (all)	2	3	1
Cardiac disorders			
CARDIAC FAILURE			
subjects affected / exposed	0 / 16 (0.00%)	1 / 29 (3.45%)	1 / 13 (7.69%)
occurrences (all)	0	2	2
RIGHT VENTRICULAR FAILURE			
subjects affected / exposed	0 / 16 (0.00%)	1 / 29 (3.45%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
TACHYCARDIA			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
Nervous system disorders			
AGEUSIA			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
DYSGEUSIA			
subjects affected / exposed	1 / 16 (6.25%)	3 / 29 (10.34%)	2 / 13 (15.38%)
occurrences (all)	1	4	3
HEADACHE			
subjects affected / exposed	2 / 16 (12.50%)	4 / 29 (13.79%)	2 / 13 (15.38%)
occurrences (all)	2	4	2
HYPOAESTHESIA			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
HYPOGEUSIA			

subjects affected / exposed	0 / 16 (0.00%)	1 / 29 (3.45%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
NEURALGIA			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
POLYNEUROPATHY			
subjects affected / exposed	0 / 16 (0.00%)	1 / 29 (3.45%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
PARAESTHESIA			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
ORTHOSTATIC INTOLERANCE			
subjects affected / exposed	0 / 16 (0.00%)	1 / 29 (3.45%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
TREMOR			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
SYNCOPE			
subjects affected / exposed	0 / 16 (0.00%)	1 / 29 (3.45%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	4 / 16 (25.00%)	11 / 29 (37.93%)	7 / 13 (53.85%)
occurrences (all)	4	18	14
HAEMORRHAGIC DIATHESIS			
subjects affected / exposed	0 / 16 (0.00%)	1 / 29 (3.45%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
NEUTROPENIA			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
Eye disorders			
EYELID OEDEMA			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
Gastrointestinal disorders			

ABDOMINAL PAIN			
subjects affected / exposed	2 / 16 (12.50%)	2 / 29 (6.90%)	0 / 13 (0.00%)
occurrences (all)	2	2	0
ABDOMINAL PAIN LOWER			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
APHTHOUS ULCER			
subjects affected / exposed	0 / 16 (0.00%)	1 / 29 (3.45%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
DIARRHOEA			
subjects affected / exposed	6 / 16 (37.50%)	9 / 29 (31.03%)	3 / 13 (23.08%)
occurrences (all)	6	10	4
CONSTIPATION			
subjects affected / exposed	1 / 16 (6.25%)	2 / 29 (6.90%)	1 / 13 (7.69%)
occurrences (all)	1	2	1
ASCITES			
subjects affected / exposed	0 / 16 (0.00%)	1 / 29 (3.45%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
DRY MOUTH			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
GASTROOESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	0 / 16 (0.00%)	1 / 29 (3.45%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
FLATULENCE			
subjects affected / exposed	0 / 16 (0.00%)	1 / 29 (3.45%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
DYSPHAGIA			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
ORAL DISCOMFORT			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
NAUSEA			

subjects affected / exposed	3 / 16 (18.75%)	9 / 29 (31.03%)	6 / 13 (46.15%)
occurrences (all)	4	10	6
LIP ULCERATION			
subjects affected / exposed	0 / 16 (0.00%)	1 / 29 (3.45%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
ORAL PAIN			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
SALIVARY HYPERSECRETION			
subjects affected / exposed	0 / 16 (0.00%)	1 / 29 (3.45%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
STOMATITIS			
subjects affected / exposed	2 / 16 (12.50%)	9 / 29 (31.03%)	7 / 13 (53.85%)
occurrences (all)	3	15	12
VOMITING			
subjects affected / exposed	2 / 16 (12.50%)	2 / 29 (6.90%)	0 / 13 (0.00%)
occurrences (all)	3	3	0
Skin and subcutaneous tissue disorders			
ECZEMA			
subjects affected / exposed	2 / 16 (12.50%)	3 / 29 (10.34%)	1 / 13 (7.69%)
occurrences (all)	2	4	2
DRY SKIN			
subjects affected / exposed	0 / 16 (0.00%)	2 / 29 (6.90%)	2 / 13 (15.38%)
occurrences (all)	0	2	2
DECUBITUS ULCER			
subjects affected / exposed	1 / 16 (6.25%)	2 / 29 (6.90%)	1 / 13 (7.69%)
occurrences (all)	1	2	1
ONYCHOCLASIS			
subjects affected / exposed	0 / 16 (0.00%)	1 / 29 (3.45%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
PRURITUS			
subjects affected / exposed	3 / 16 (18.75%)	8 / 29 (27.59%)	5 / 13 (38.46%)
occurrences (all)	3	8	5
RASH			
subjects affected / exposed	3 / 16 (18.75%)	5 / 29 (17.24%)	2 / 13 (15.38%)
occurrences (all)	4	6	2

Renal and urinary disorders			
INCONTINENCE			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
NEPHROSCLEROSIS			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
PROTEINURIA			
subjects affected / exposed	1 / 16 (6.25%)	2 / 29 (6.90%)	1 / 13 (7.69%)
occurrences (all)	1	2	1
RENAL FAILURE			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	2 / 16 (12.50%)	6 / 29 (20.69%)	4 / 13 (30.77%)
occurrences (all)	2	8	6
BACK PAIN			
subjects affected / exposed	0 / 16 (0.00%)	2 / 29 (6.90%)	2 / 13 (15.38%)
occurrences (all)	0	2	2
BONE PAIN			
subjects affected / exposed	0 / 16 (0.00%)	2 / 29 (6.90%)	2 / 13 (15.38%)
occurrences (all)	0	2	2
FLANK PAIN			
subjects affected / exposed	1 / 16 (6.25%)	2 / 29 (6.90%)	1 / 13 (7.69%)
occurrences (all)	1	2	1
GROIN PAIN			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
JOINT EFFUSION			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
MUSCLE SPASMS			
subjects affected / exposed	0 / 16 (0.00%)	1 / 29 (3.45%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
OSTEONECROSIS OF JAW			

subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
OSTEOCHONDROSIS			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
PAIN IN EXTREMITY			
subjects affected / exposed	0 / 16 (0.00%)	2 / 29 (6.90%)	2 / 13 (15.38%)
occurrences (all)	0	2	2
Infections and infestations			
CONJUNCTIVITIS			
subjects affected / exposed	0 / 16 (0.00%)	1 / 29 (3.45%)	1 / 13 (7.69%)
occurrences (all)	0	2	2
CANDIDA INFECTION			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
BRONCHITIS			
subjects affected / exposed	0 / 16 (0.00%)	1 / 29 (3.45%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
NASOPHARYNGITIS			
subjects affected / exposed	1 / 16 (6.25%)	2 / 29 (6.90%)	1 / 13 (7.69%)
occurrences (all)	1	2	1
PERITONITIS			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
PHARYNGITIS			
subjects affected / exposed	0 / 16 (0.00%)	1 / 29 (3.45%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 16 (0.00%)	1 / 29 (3.45%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
RHINITIS			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
URINARY TRACT INFECTION			
subjects affected / exposed	2 / 16 (12.50%)	4 / 29 (13.79%)	2 / 13 (15.38%)
occurrences (all)	2	4	2

URINARY TRACT INFECTION STAPHYLOCOCCAL			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	5 / 16 (31.25%)	10 / 29 (34.48%)	5 / 13 (38.46%)
occurrences (all)	5	11	6
CACHEXIA			
subjects affected / exposed	0 / 16 (0.00%)	1 / 29 (3.45%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
DEHYDRATION			
subjects affected / exposed	0 / 16 (0.00%)	1 / 29 (3.45%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
DIABETES MELLITUS			
subjects affected / exposed	0 / 16 (0.00%)	2 / 29 (6.90%)	2 / 13 (15.38%)
occurrences (all)	0	3	3
HYPERGLYCAEMIA			
subjects affected / exposed	3 / 16 (18.75%)	4 / 29 (13.79%)	1 / 13 (7.69%)
occurrences (all)	4	6	2
HYPERKALAEMIA			
subjects affected / exposed	0 / 16 (0.00%)	2 / 29 (6.90%)	2 / 13 (15.38%)
occurrences (all)	0	3	3
HYPOALBUMINAEMIA			
subjects affected / exposed	0 / 16 (0.00%)	1 / 29 (3.45%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
HYPERURICAEMIA			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
HYPERTRIGLYCERIDAEMIA			
subjects affected / exposed	3 / 16 (18.75%)	3 / 29 (10.34%)	0 / 13 (0.00%)
occurrences (all)	3	3	0
HYPOCALCAEMIA			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
HYPOMAGNESAEMIA			

subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
HYPOKALAEMIA			
subjects affected / exposed	1 / 16 (6.25%)	2 / 29 (6.90%)	1 / 13 (7.69%)
occurrences (all)	1	2	1
HYPOCHLORAEMIA			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	2	2	0
HYPONATRAEMIA			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
HYPOPHOSPHATAEMIA			
subjects affected / exposed	2 / 16 (12.50%)	2 / 29 (6.90%)	0 / 13 (0.00%)
occurrences (all)	2	2	0
PROTEIN DEFICIENCY			
subjects affected / exposed	1 / 16 (6.25%)	1 / 29 (3.45%)	0 / 13 (0.00%)
occurrences (all)	1	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 January 2012	Amendment 1: was released before inclusion of any patients due to a deficiency report dated 06-Jan-2012 received from the German "Bundesinstitut für Arzneimittel und Medizinprodukte" (BfArM) during initial submission of this trial. All patients with impaired liver function (Child-Pugh class A, B, or C) were excluded from the study (added as an exclusion criterion). The reporting of positive hepatitis B virus (HBV) and hepatitis C virus (HCV) testing to health authorities was described. Furthermore, specifications regarding oral contraceptives were included.
11 November 2013	Amendment 2: included: 1) adjustment of the number of involved trial sites to increase the recruitment rate, 2) a specification of the time point of survival analysis in the data analysis section (it was explained in the data analysis section that survival analysis will be performed 12 months after LPFV, as already stated in the protocol synopsis), 3) the adaption of the study protocol to the current SmPC (introduction of the Everolimus 2.5 mg tablet and adaption of the dose modification rules with the SmPC update in July 2013), 4) minor changes regarding sponsor 's responsible personnel
28 April 2015	Amendment 3: mainly included the rationale for early termination of enrollment due to the low recruitment rate (effective with approval by institutional review boards/independent ethics committees (IRBs/IECs) and health authorities). Furthermore, administrative changes were implemented.

Notes:

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.

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.

Notes: