Clinical trial results:
5, 6 or 7 year follow-up control after the SCHEDULE study (SCANDINAVIAN HEART TRANSPLANT EVEROLIMUS DE NOVO STUDY WITH EARLY CNI AVOIDANCE)

Summary

EudraCT number	2016-000404-28
Trial protocol	SE DK
Global end of trial date	25 September 2017

Results information

Result version number	v1 (current)
This version publication date	11 October 2018
First version publication date	11 October 2018

Trial information

Trial identification

Sponsor protocol code	CRAD001ANO05

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02864706
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharmaceuticals
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharmaceuticals, 41 613241111, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharmaceuticals, 41 613241111, Novartis.email@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	25 September 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 September 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Renal function as assessed by measured glomerular filtration rate (mGFR)

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	18 January 2016
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	Norway: 44
Country: Number of subjects enrolled	Sweden: 28
Country: Number of subjects enrolled	Denmark: 23
Worldwide total number of subjects	95
EEA total number of subjects	95

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)	86
From 65 to 84 years	9

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

49 Patients were enrolled in the study, but 1 patient withdrew consent in the Everolimus arm.

Pre-assignment

Screening details:

The Safety Set had 48 patients in the Everolimus arm and 47 in the Control arm. The Intent to Treat set had 46 in the Everolimus arm and 47 in the Control arm. 48 started the Everolimus arm but 2 patients were excluded from ITT at month 12 due to missing measured GFR.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Everolimus

Arm description:

All participants who were included in the initial core study SCHEDULE (CRAD001ANO02) who started immunosuppressive regimen consisting of low dose CsA, everolimus, MMF and CS. After week 11, the participants regimen consisted of everolimus, MMF and CS and were extended per protocol

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:

All participants who were included in the initial core study SCHEDULE (CRAD001ANO02) who started immunosuppressive regimen consisting of low dose CsA, everolimus, MMF and CS. After week 11, the participants regimen consisted of everolimus, MMF and CS and were extended per proto

Arm title	Control

Arm description:

All participants who were included in the initial core study SCHEDULE (CRAD001ANO02) who received an immunosuppressive regimen consisting of CsA, MMF and CS throughout the study.

Arm type	Active comparator
Investigational medicinal product name	Standard of Care
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants who were included in core study SCHEDULE (CRAD001ANO02) who started immunosuppressive
regimen consisting of low dose CsA, everolimus, MMF and CS. After week 11, CsA was discontinued.

Number of subjects in period 1	Everolimus	Control
Started	48	47
Completed	48	47

Baseline characteristics

Reporting groups	
Reporting group title	Everolimus
Reporting group description:	
All participants who were included in the initial core study SCHEDULE (CRAD001ANO02) who started immunosuppressive regimen consisting of low dose CsA, everolimus, MMF and CS. After week 11, the participants regimen consisted of everolimus, MMF and CS and were extended per protocol	
Reporting group title	Control
Reporting group description:	
All participants who were included in the initial core study SCHEDULE (CRAD001ANO02) who received an immunosuppressive regimen consisting of CsA, MMF and CS throughout the study.	

Reporting group values	Everolimus	Control	Total
Number of subjects	48	47	95
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)	43	43	86
From 65-84 years	5	4	9
85 years and over	0	0	0
Age Continuous Units: Participants			
arithmetic mean	50.13	52.11	
standard deviation	± 13.43	± 11.61	-
Sex: Female, Male Units: Subjects			
Female	13	12	25
Male	35	35	70
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	2	3
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	1	1
White	47	44	91
More than one race	0	0	0
Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	Everolimus
Reporting group description:	
All participants who were included in the initial core study SCHEDULE (CRAD001ANO02) who started immunosuppressive regimen consisting of low dose CsA, everolimus, MMF and CS. After week 11, the participants regimen consisted of everolimus, MMF and CS and were extended per protocol	
Reporting group title	Control
Reporting group description:	
All participants who were included in the initial core study SCHEDULE (CRAD001ANO02) who received an immunosuppressive regimen consisting of CsA, MMF and CS throughout the study.	

Primary: Measured Glomerular Filtration Rate (mGFR)

End point title	Measured Glomerular Filtration Rate (mGFR)
End point description:	
Renal function as assessed by measured Glomerular Filtration Rate (mGFR) (Cr-EDTA or iohexol clearance). Baseline Visit 1 and Patient 4252 excluded from the intent treat analysis set.	
End point type	Primary
End point timeframe:	
at the 5-7 year follow-up visit	

End point values	Everolimus	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	46		
Units: mL/min/1.73m2				
least squares mean (standard deviation)	74.7 (± 23.3)	62.4 (± 16.5)		

Statistical analyses

Statistical analysis title	Measured Glomerular Filtration Rate
Comparison groups	Everolimus v Control
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0043
Method	ANCOVA

Secondary: Progression of Cardiac allograft vasculopathy (CAV) recorded by Intravascular Ultrasound (IVUS)

End point title	Progression of Cardiac allograft vasculopathy (CAV) recorded by Intravascular Ultrasound (IVUS)

End point description:

Cardiac Allograft Vasculopathy (CAV) was defined as mean maximal intimal thickness (MIT) ≥0.5 mm, measured for the entire matched pullback recording by intravascular ultrasound (IVUS). The incidence of CAV at 5-7 years was compared between groups using the Cochran-Mantel-Haenszel test with stratification according to baseline distribution of CAV incidence.

End point type	Secondary

End point timeframe:

within 5-7 years

End point values	Everolimus	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	35		
Units: mm				
arithmetic mean (standard deviation)	0.13 (± 0.15)	0.23 (± 0.24)		

Statistical analyses

Statistical analysis title	Cardiac Allograft Vasculopathy (CAV)
Comparison groups	Everolimus v Control
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.037
Method	Cochran-Mantel-Haenszel

Secondary: Percent of Participants with Incidence of Coronary Allograft Vasculopathy (CAV)

End point title	Percent of Participants with Incidence of Coronary Allograft Vasculopathy (CAV)

End point description:

Cardiac Allograft Vasculopathy (CAV) was defined as mean maximal intimal thickness (MIT) ≥0.5 mm, measured for the entire matched pullback recording by intravascular ultrasound (IVUS). The incidence of CAV at 5-7 years was compared between groups using the Cochran-Mantel-Haenszel test with stratification according to baseline distribution of CAV incidence.

End point type	Secondary

End point timeframe:

at the 5-7 year follow-up

End point values	Everolimus	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	35		
Units: percent of participants	53	74		

Statistical analyses

No statistical analyses for this end point

Secondary: Myocardial structure and function

End point title	Myocardial structure and function

End point description:

Myocardial structure and function by echocardiography assessment measured by ventricular end systolic diameter.

End point type	Secondary

End point timeframe:

within 5-7 years

End point values	Everolimus	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	47		
Units: cm				
arithmetic mean (standard deviation)				
LVESD (left ventricular end systolic diameter)|	3.1 (± 0.8)	3.1 (± 0.6)		
LVEDD (left ventricular end diastolic diameter)|	4.7 (± 0.6)	4.9 (± 0.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of life by SF-36 change from pre-transplantation to 5-7 year follow-up

End point title	Quality of life by SF-36 change from pre-transplantation to 5-7 year follow-up

End point description:

This Quality of life Short Form Survey with 36 items (Minnesota Living with Heart Failure Questionnaire)was administered to patients pre-transplantation and after transplantation at the 5-7 year visit. This data represents the change. The survey consist of scores on a scale. Each form is scaled from 0 t 100. 0 = maximum disability and 100 equals no disability.

End point type	Secondary

End point timeframe:

at the 5-7 year visit

End point values	Everolimus	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	47		
Units: scores on a scale				
arithmetic mean (standard deviation)				
Physical Health Summary|	16.8 (± 15.0)	13.2 (± 13.3)		
Mental Health Summary|	10.4 (± 10.5)	15.3 (± 15.5)		
Physical Functioning|	36.7 (± 38.4)	40.8 (± 30.4)		
Role Physical|	50.2 (± 32.3)	55.1 (± 32.4)		
Bodily Pain|	10.3 (± 34.8)	7.2 (± 34.1)		
General Health|	25.7 (± 26.4)	23.4 (± 25.6)		
Vitality|	30.0 (± 25.8)	28.9 (± 29.0)		
Social Functioning|	39.9 (± 31.5)	43.9 (± 32.4)		
Role Emotional|	23.8 (± 36.7)	42.8 (± 46.5)		
Mental Health|	8.6 (± 17.2)	14.4 (± 25.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the Euro Quality of Life 5D

End point title	Change from baseline in the Euro Quality of Life 5D

End point description:

Change from baseline in Euro Quality of Life-5D from 3 Year Follow-Up to 5 to 7 Year Follow-Up Baseline Visit 1 (ITT Set) The EQ-5D is a self-reported questionnaire that describes a respondent's health using a descriptive system comprised of five items, each representing a different health dimension (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). For each dimension, respondents state whether they have no problems, slight problems, moderate problems, severe problems, or are unable to perform the activity.

End point type	Secondary

End point timeframe:

Baseline, 5-7 year visit

End point values	Everolimus	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	46		
Units: scores on the scale				
arithmetic mean (standard deviation)	0.2323 (± 0.3849)	0.2982 (± 0.3274)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in visual analog scale (VAS)

End point title	Change from baseline in visual analog scale (VAS)

End point description:

Change in visual analog scale (VAS) from baseline to the 5 to 7 Year follow up visit. 0 is no pain; and 10 is the worst possible pain

End point type	Secondary

End point timeframe:

baseline, at the 5-7 year visit

End point values	Everolimus	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	47		
Units: mm				
arithmetic mean (standard deviation)	35.6 (± 26.9)	34.0 (± 32.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with Beck Depression Inventory (BDI)

End point title	Number of participants with Beck Depression Inventory (BDI)

End point description:

Beck Depression Inventory (BDI) Score has the following categories of depression. Normal, Mild, Moderate Severe and Missing.

End point type	Secondary

End point timeframe:

at the 5-7 year visit

End point values	Everolimus	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	47		
Units: participants				
Normal|	15	13		
Mild|	6	4		
Moderate|	2	5		
Severe|	1	0		
Missing|	3	5		

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	19.1

Reporting groups

Reporting group title	Everolimus

Reporting group description:

Everolimus

Reporting group title	Control

Reporting group description:

Control

Serious adverse events	Everolimus	Control	
Total subjects affected by serious adverse events			
subjects affected / exposed	26 / 48 (54.17%)	18 / 47 (38.30%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 48 (2.08%)	2 / 47 (4.26%)	
occurrences causally related to treatment / all	2 / 2	7 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	1 / 48 (2.08%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	1 / 1	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine cancer			
subjects affected / exposed	0 / 48 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm			

subjects affected / exposed	1 / 48 (2.08%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Hernia			
subjects affected / exposed	1 / 48 (2.08%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 48 (2.08%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	6 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Heart transplant rejection			
subjects affected / exposed	0 / 48 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	2 / 48 (4.17%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	11 / 11	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	1 / 48 (2.08%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	5 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 48 (2.08%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			

subjects affected / exposed	1 / 48 (2.08%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	0 / 48 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 48 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	1 / 48 (2.08%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	6 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 48 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	1 / 48 (2.08%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	6 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 48 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	2 / 48 (4.17%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	6 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress cardiomyopathy			

subjects affected / exposed	1 / 48 (2.08%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	8 / 8	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 48 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	12 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	2 / 48 (4.17%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	12 / 12	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal detachment			
subjects affected / exposed	1 / 48 (2.08%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 48 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	12 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fissure			
subjects affected / exposed	0 / 48 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	10 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 48 (0.00%)	2 / 47 (4.26%)	
occurrences causally related to treatment / all	0 / 0	11 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food poisoning			
subjects affected / exposed	0 / 48 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Large intestinal stenosis			
subjects affected / exposed	1 / 48 (2.08%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	6 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctalgia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	10 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal perforation			
subjects affected / exposed	1 / 48 (2.08%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	6 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 48 (2.08%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	5 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	1 / 48 (2.08%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudarthrosis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column stenosis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Pneumonia			
subjects affected / exposed	13 / 48 (27.08%)	3 / 47 (6.38%)	
occurrences causally related to treatment / all	72 / 72	52 / 52	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	2 / 48 (4.17%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	12 / 12	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 48 (2.08%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	13 / 13	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 48 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	13 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	13 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 48 (4.17%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	12 / 12	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	2 / 48 (4.17%)	2 / 47 (4.26%)	
occurrences causally related to treatment / all	6 / 6	27 / 27	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	0 / 48 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 48 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	13 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Everolimus	Control	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 48 (31.25%)	4 / 47 (8.51%)	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	5 / 48 (10.42%)	0 / 47 (0.00%)	
occurrences (all)	21	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 48 (8.33%)	3 / 47 (6.38%)	
occurrences (all)	23	24	
Infections and infestations			
Pneumonia			
subjects affected / exposed	8 / 48 (16.67%)	2 / 47 (4.26%)	
occurrences (all)	46	14	
Sepsis			
subjects affected / exposed	3 / 48 (6.25%)	0 / 47 (0.00%)	
occurrences (all)	16	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 June 2016	New global study code Ensure that data from already occurred 5 or 6 years routine annual visits can be collected.
07 July 2016	Updated according to comments from the Danish HA to initial protocol v2.0 (Definitions for (S)AE, ADR, SUSAR)

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.

There is no investigational medicinal product (IMP). This study is a single follow-up visit. Hence patients' first and last visit dates are the same. And thus, there are no Adverse Events.

Notes: