Clinical trial results:
A multi-center, randomized, open-label, parallel group study investigating the renal tolerability, efficacy and safety of a CNI-free regimen (everolimus and MPA) versus a CNI-regimen with everolimus in heart transplant recipients

Summary

EudraCT number	2007-002671-14
Trial protocol	DE
Global end of trial date	06 March 2017

Results information

Result version number	v1 (current)
This version publication date	22 March 2018
First version publication date	22 March 2018

Trial information

Trial identification

Sponsor protocol code	CRAD001ADE14

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00862979
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	06 March 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 March 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to demonstrate superiority of a CNI-free regimen with respect to the renal function at Month 18 post-transplant, assessed by glomerular filtration rate (GFR) (MDRD method) as compared to the standard CNI-based regimen in HTx patients.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 February 2009
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: 162
Worldwide total number of subjects	162
EEA total number of subjects	162

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)	155
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

232 patients were screened, of these , 193 patients were included in safety set which included 31 non-randomized and 162 randomized. Of these, 145 patients were treated with study medication and had at least 1 post-baseline assessment of the primary outcome variable and included in the Full Analysis Set FAS.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Arms

Are arms mutually exclusive?	Yes
Arm title	CNI-regimen

Arm description:

CNI-regimen: cyclosporine A (CyA) or tacrolimus (TAC) with everolimus (EVR) with corticosteroids

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

Dosage and administration details:

0.25mg, 0.75mg or 1.0mg based on blood levels (5-10 ng/mL) per day

Investigational medicinal product name	tacrolimus
Investigational medicinal product code	
Other name	Prograf, TAC
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

0.5 mg, 1 mg, or 5 mg capsule given according to blood levels

Investigational medicinal product name	Cyclosporine A
Investigational medicinal product code	
Other name	Sandimmun® Optoral, CyA
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

10 mg, 25 mg, 50 mg or 100 mg capsule according to blood levels

Arm title	CNI-free-regimen

Arm description:

CNI-free regimen: everolimus (EVR) with MPA (either MMF or enteric coated mycophenolate sodium (EC-MPS)) and corticosteroids

Arm type	Experimental

Investigational medicinal product name	Everolimus
Investigational medicinal product code	RAD001
Other name	Certican
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

0.25mg, 0.75mg or 1.0mg based on blood levels (5-10 ng/mL) per day

Investigational medicinal product name	Cyclosporine A
Investigational medicinal product code	
Other name	Sandimmun® Optoral, CyA
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

10 mg, 25 mg, 50 mg or 100 mg capsule according to blood levels dispense on month 6 to 9 only

Investigational medicinal product name	tacrolimus
Investigational medicinal product code	
Other name	Prograf, TAC
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

0.5 mg, 1 mg, or 5 mg capsule given according to blood levels dispense on month 6 to 9 only

Investigational medicinal product name	Enteric coated mycophenolate sodium
Investigational medicinal product code	
Other name	Myfortic, EC-MPS
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

180 mg or 360 mg tablet dosed 1440-2280 mg per day

Investigational medicinal product name	mycophenolate mofetil
Investigational medicinal product code	
Other name	CellCept, MMF
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

250 mg or 500 mg tablets with a dose of 1500-3000 mg per da

Number of subjects in period 1	CNI-regimen	CNI-free-regimen
Started	84	78
Completed	76	71
Not completed	8	7
Adverse event, serious fatal	-	1
Patient withdrew consent	2	1
Adverse event, non-fatal	6	3
Administrative problems	-	1

Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	CNI-regimen
Reporting group description:	
CNI-regimen: cyclosporine A (CyA) or tacrolimus (TAC) with everolimus (EVR) with corticosteroids	
Reporting group title	CNI-free-regimen
Reporting group description:	
CNI-free regimen: everolimus (EVR) with MPA (either MMF or enteric coated mycophenolate sodium (EC-MPS)) and corticosteroids	

Reporting group values	CNI-regimen	CNI-free-regimen	Total
Number of subjects	84	78	162
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)	81	74	155
From 65-84 years	3	4	7
85 years and over	0	0	0
Age Continuous			
Units: years			
arithmetic mean	52.7	50.3	
standard deviation	± 9.7	± 9.8	-
Sex: Female, Male			
Units: Subjects			
Female	11	13	24
Male	73	65	138

End points

End points reporting groups

Reporting group title	CNI-regimen
Reporting group description:	
CNI-regimen: cyclosporine A (CyA) or tacrolimus (TAC) with everolimus (EVR) with corticosteroids	
Reporting group title	CNI-free-regimen
Reporting group description:	
CNI-free regimen: everolimus (EVR) with MPA (either MMF or enteric coated mycophenolate sodium (EC-MPS)) and corticosteroids	

Primary: Calculated Glomerular Filtration Rate (cGFR) Using Modification of Diet in Renal Disease (MDRD) Formula at Month 18

End point title	Calculated Glomerular Filtration Rate (cGFR) Using Modification of Diet in Renal Disease (MDRD) Formula at Month 18
End point description:	
Calculated Glomerular Filtration Rate (cGFR) Using Modification of Diet in Renal Disease (MDRD) Formula at Month 18 cGFR (in mL/min/1.73 m2) = 186.3*(C-1.154)*(A-0.203)*G*R where C = the serum concentration of creatinine (mg/dL), A = age (years), G = 0.742 when gender is female, otherwise G = 1, R = 1.21 when race is black, otherwise R = 1.	
End point type	Primary
End point timeframe:	
Month 18	

End point values	CNI-regimen	CNI-free-regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	65		
Units: mL/min				
arithmetic mean (standard deviation)	54.2 (± 17.9)	66.9 (± 23.0)		

Statistical analyses

Statistical analysis title	cGFR using MDRD Formula at Month 18
Comparison groups	CNI-regimen v CNI-free-regimen
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-11.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.5
upper limit	-6.1

Secondary: Occurrence of treatment failures from Month 6 to 9 and Month 9 to 18

End point title	Occurrence of treatment failures from Month 6 to 9 and Month 9 to 18

End point description:

Treatment failure was defined as composite endpoint of biopsy proven acute rejection of ISHLT 1990 grade ≥ 3A resp. ISHLT 2004 grade ≥ 2R, acute rejection episodes associated with hemodynamic compromise, graft loss / re-transplant, death, loss to follow up (at least one condition must be present). If participant had an occurrence in each period it was counted for each period.

End point type	Secondary

End point timeframe:

Month 6 to Month 9; Month 9 to Month 18

End point values	CNI-regimen	CNI-free-regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	74		
Units: Occurences				
Month 6 to Month 9 Treatment failure-all reasons	1	4		
Month 9 to Month 18 Treatment failure-all reasons	3	15		

Statistical analyses

Statistical analysis title	Occurrence of treatment failures from Month 6 to 9

Statistical analysis description:

Month 6 to Month 9

Comparison groups	CNI-regimen v CNI-free-regimen
Number of subjects included in analysis	148
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.203
Method	Fisher exact

Statistical analysis title	Occurrence of treatment failures from Month 9-18

Statistical analysis description:

Month 9 to Month 18

Comparison groups	CNI-regimen v CNI-free-regimen
Number of subjects included in analysis	148
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.002
Method	Fisher exact

Secondary: Occurrence of major cardiac events (MACE) from Month 6 to 18

End point title	Occurrence of major cardiac events (MACE) from Month 6 to 18

End point description:

Major cardiac events (MACE) was defined as one of the following: any death, myocardial infarction, coronary artery bypass grafting

End point type	Secondary

End point timeframe:

Month 6 to Month 18

End point values	CNI-regimen	CNI-free-regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	71		
Units: Occurences				
Myocardial infarction|	1	0		
Death|	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Calculated Glomerular Filtration Rate (cGFR) according to Cockcroft-Gault at Month 12 and 18

End point title	Calculated Glomerular Filtration Rate (cGFR) according to Cockcroft-Gault at Month 12 and 18

End point description:

Calculated Glomerular Filtration Rate (cGFR) according to Cockcroft-Gault at Month 12 and 18. For men: GFR=(140-Age) x Body weight (kg) / 72 x Serum Creatinine (mg/dl) For women: GFR=0.85 (140 -Age) x Body weight(kg)/ 72 x Serum Creatinine (mg/dl)

End point type	Secondary

End point timeframe:

Month 12 and 18

End point values	CNI-regimen	CNI-free-regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	71		
Units: mL/min				
arithmetic mean (standard deviation)				
Month 12 n=68, 62|	54.2 (± 19.7)	69.8 (± 23.4)		
Month 18 n=69, 65|	54.2 (± 17.9)	66.9 (± 23.00)		

Statistical analyses

Statistical analysis title	cGFR according to Cockcroft-Gault at Month 12
Statistical analysis description: Month 12	
Comparison groups	CNI-regimen v CNI-free-regimen
Number of subjects included in analysis	145
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.6
upper limit	-8.3

Statistical analysis title	cGFR according to Cockcroft-Gault at Month 18
Statistical analysis description: Month 18	
Comparison groups	CNI-regimen v CNI-free-regimen
Number of subjects included in analysis	145
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-11.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.5
upper limit	-6.1

Secondary: Serum Creatinine at Month 6, 8, 9, 10 12 and 18

End point title	Serum Creatinine at Month 6, 8, 9, 10 12 and 18

End point description:

Serum Creatinine is an indicator of renal function measured in the blood

End point type	Secondary

End point timeframe:

Month 6, 8, 9, 10 12 and 18

End point values	CNI-regimen	CNI-free-regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	71		
Units: µmol/L				
arithmetic mean (standard deviation)				
Month 6|	1.53 (± 0.49)	1.49 (± 0.51)		
Month 8 n=73, 70|	1.44 (± 0.41)	1.27 (± 0.35)		
Month 9 n=74, 70|	1.58 (± 0.75)	1.24 (± 0.32)		
Month 10 n=74, 70|	1.53 (± 0.53)	1.20 (± 0.30)		
Month 12 n=74, 70|	1.53 (± 0.52)	1.22 (± 0.33)		
Month 18|	1.50 (± 0.50)	1.27 (± 0.44)		

Statistical analyses

No statistical analyses for this end point

Secondary: Reciprocal Creatinine Slope between Month 6 and Month 18

End point title	Reciprocal Creatinine Slope between Month 6 and Month 18

End point description:

Reciprocal Creatinine Slope is an indication of renal function over time with a higher slope value indicating an improvement in renal function.

End point type	Secondary

End point timeframe:

Between Month 6 and Month 18

End point values	CNI-regimen	CNI-free-regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	71		
Units: 1/serum vs time				
arithmetic mean (standard deviation)	0.045 (± 0.364)	0.403 (± 1.863)		

Statistical analyses

Statistical analysis title	Reciprocal Creatinine Slope between Month 6&18
Comparison groups	CNI-regimen v CNI-free-regimen
Number of subjects included in analysis	145
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.008
Method	Wilcoxon (Mann-Whitney)

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 reported in this record are from date of First Patient First Treatment until Last Patient Last Visit

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	20.0

Reporting groups

Reporting group title	CNI-Regimen
Reporting group description:	
CNI-Regimen	
Reporting group title	CNI-free-regimen
Reporting group description:	
CNI-free-regimen	

Serious adverse events	CNI-Regimen	CNI-free-regimen	
Total subjects affected by serious adverse events			
subjects affected / exposed	40 / 84 (47.62%)	29 / 78 (37.18%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B-CELL LYMPHOMA			
subjects affected / exposed	1 / 84 (1.19%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BLADDER CANCER			
subjects affected / exposed	1 / 84 (1.19%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PLASMACYTOMA			

subjects affected / exposed	1 / 84 (1.19%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PROSTATE CANCER RECURRENT			
subjects affected / exposed	0 / 84 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
ANEURYSM			
subjects affected / exposed	0 / 84 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANGIOPATHY			
subjects affected / exposed	1 / 84 (1.19%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEEP VEIN THROMBOSIS			
subjects affected / exposed	3 / 84 (3.57%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERTENSION			
subjects affected / exposed	1 / 84 (1.19%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
MEDICAL DEVICE REMOVAL			
subjects affected / exposed	1 / 84 (1.19%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
CHEST PAIN			
subjects affected / exposed	1 / 84 (1.19%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

CHILLS			
subjects affected / exposed	0 / 84 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FATIGUE			
subjects affected / exposed	0 / 84 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
OEDEMA			
subjects affected / exposed	1 / 84 (1.19%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OEDEMA PERIPHERAL			
subjects affected / exposed	1 / 84 (1.19%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYREXIA			
subjects affected / exposed	0 / 84 (0.00%)	2 / 78 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
STENOSIS			
subjects affected / exposed	1 / 84 (1.19%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
HEART TRANSPLANT REJECTION			
subjects affected / exposed	3 / 84 (3.57%)	7 / 78 (8.97%)	
occurrences causally related to treatment / all	0 / 3	7 / 8	
deaths causally related to treatment / all	0 / 0	0 / 1	
Reproductive system and breast disorders			
BENIGN PROSTATIC HYPERPLASIA			
subjects affected / exposed	0 / 84 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
DYSPNOEA			
subjects affected / exposed	1 / 84 (1.19%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY EMBOLISM			
subjects affected / exposed	1 / 84 (1.19%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY MASS			
subjects affected / exposed	1 / 84 (1.19%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
BLOOD CREATININE INCREASED			
subjects affected / exposed	1 / 84 (1.19%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-REACTIVE PROTEIN INCREASED			
subjects affected / exposed	2 / 84 (2.38%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMOGLOBIN DECREASED			
subjects affected / exposed	1 / 84 (1.19%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFLAMMATORY MARKER INCREASED			
subjects affected / exposed	1 / 84 (1.19%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
WEIGHT INCREASED			

subjects affected / exposed	1 / 84 (1.19%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
ACETABULUM FRACTURE			
subjects affected / exposed	1 / 84 (1.19%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUMBAR VERTEBRAL FRACTURE			
subjects affected / exposed	1 / 84 (1.19%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VASCULAR PSEUDOANEURYSM			
subjects affected / exposed	1 / 84 (1.19%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
ATRIAL FIBRILLATION			
subjects affected / exposed	0 / 84 (0.00%)	3 / 78 (3.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
ATRIAL FLUTTER			
subjects affected / exposed	0 / 84 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CORONARY ARTERY STENOSIS			
subjects affected / exposed	1 / 84 (1.19%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LEFT VENTRICULAR DYSFUNCTION			
subjects affected / exposed	1 / 84 (1.19%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

PERICARDIAL EFFUSION			
subjects affected / exposed	0 / 84 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SINUS TACHYCARDIA			
subjects affected / exposed	1 / 84 (1.19%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TACHYCARDIA			
subjects affected / exposed	0 / 84 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
MYOCLONIC EPILEPSY			
subjects affected / exposed	1 / 84 (1.19%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SCIATICA			
subjects affected / exposed	0 / 84 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SYNCOPE			
subjects affected / exposed	2 / 84 (2.38%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	2 / 84 (2.38%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
EYE PAIN			

subjects affected / exposed	0 / 84 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GLAUCOMA			
subjects affected / exposed	0 / 84 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
ABDOMINAL HERNIA			
subjects affected / exposed	1 / 84 (1.19%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
APHTHOUS ULCER			
subjects affected / exposed	0 / 84 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COLITIS ISCHAEMIC			
subjects affected / exposed	0 / 84 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA			
subjects affected / exposed	1 / 84 (1.19%)	2 / 78 (2.56%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
INGUINAL HERNIA			
subjects affected / exposed	1 / 84 (1.19%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NAUSEA			
subjects affected / exposed	1 / 84 (1.19%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VOMITING			

subjects affected / exposed	1 / 84 (1.19%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
CHOLECYSTITIS			
subjects affected / exposed	1 / 84 (1.19%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLECYSTITIS ACUTE			
subjects affected / exposed	1 / 84 (1.19%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLECYSTITIS CHRONIC			
subjects affected / exposed	1 / 84 (1.19%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLELITHIASIS			
subjects affected / exposed	2 / 84 (2.38%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
ANGIOEDEMA			
subjects affected / exposed	1 / 84 (1.19%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIABETIC FOOT			
subjects affected / exposed	1 / 84 (1.19%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SKIN HAEMORRHAGE			
subjects affected / exposed	1 / 84 (1.19%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

ACUTE KIDNEY INJURY			
subjects affected / exposed	2 / 84 (2.38%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHRONIC KIDNEY DISEASE			
subjects affected / exposed	2 / 84 (2.38%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMATURIA			
subjects affected / exposed	1 / 84 (1.19%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL ARTERY STENOSIS			
subjects affected / exposed	1 / 84 (1.19%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL FAILURE			
subjects affected / exposed	1 / 84 (1.19%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL IMPAIRMENT			
subjects affected / exposed	1 / 84 (1.19%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY RETENTION			
subjects affected / exposed	1 / 84 (1.19%)	2 / 78 (2.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
HYPERTHYROIDISM			
subjects affected / exposed	1 / 84 (1.19%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue			

disorders			
BACK PAIN			
subjects affected / exposed	0 / 84 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
OSTEOARTHRITIS			
subjects affected / exposed	1 / 84 (1.19%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OSTEOPOROSIS			
subjects affected / exposed	1 / 84 (1.19%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
ANAL ABSCESS			
subjects affected / exposed	0 / 84 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ASPERGILLOMA			
subjects affected / exposed	1 / 84 (1.19%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ASPERGILLUS INFECTION			
subjects affected / exposed	2 / 84 (2.38%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BACTERAEMIA			
subjects affected / exposed	1 / 84 (1.19%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BACTERIAL INFECTION			
subjects affected / exposed	1 / 84 (1.19%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

CAMPYLOBACTER GASTROENTERITIS			
subjects affected / exposed	1 / 84 (1.19%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CLOSTRIDIUM DIFFICILE COLITIS			
subjects affected / exposed	1 / 84 (1.19%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CYTOMEGALOVIRUS INFECTION			
subjects affected / exposed	0 / 84 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEVICE RELATED INFECTION			
subjects affected / exposed	0 / 84 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIABETIC GANGRENE			
subjects affected / exposed	0 / 84 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIVERTICULITIS			
subjects affected / exposed	2 / 84 (2.38%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENDOCARDITIS			
subjects affected / exposed	0 / 84 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ESCHERICHIA INFECTION			
subjects affected / exposed	1 / 84 (1.19%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEBRILE INFECTION			

subjects affected / exposed	1 / 84 (1.19%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROENTERITIS			
subjects affected / exposed	2 / 84 (2.38%)	2 / 78 (2.56%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROENTERITIS NOROVIRUS			
subjects affected / exposed	0 / 84 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROENTERITIS SALMONELLA			
subjects affected / exposed	1 / 84 (1.19%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GROIN INFECTION			
subjects affected / exposed	0 / 84 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
H1N1 INFLUENZA			
subjects affected / exposed	1 / 84 (1.19%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HERPES SIMPLEX			
subjects affected / exposed	0 / 84 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HERPES ZOSTER			
subjects affected / exposed	1 / 84 (1.19%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HERPES ZOSTER INFECTION NEUROLOGICAL			

subjects affected / exposed	0 / 84 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTED LYMPHOCELE			
subjects affected / exposed	0 / 84 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTION			
subjects affected / exposed	3 / 84 (3.57%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	2 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTIOUS PLEURAL EFFUSION			
subjects affected / exposed	1 / 84 (1.19%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFLUENZA			
subjects affected / exposed	0 / 84 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
OTITIS EXTERNA			
subjects affected / exposed	0 / 84 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMOCYSTIS JIROVECII PNEUMONIA			
subjects affected / exposed	2 / 84 (2.38%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			
subjects affected / exposed	6 / 84 (7.14%)	2 / 78 (2.56%)	
occurrences causally related to treatment / all	1 / 6	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEPTIC SHOCK			

subjects affected / exposed	1 / 84 (1.19%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
STAPHYLOCOCCAL INFECTION			
subjects affected / exposed	1 / 84 (1.19%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TUBERCULOSIS			
subjects affected / exposed	1 / 84 (1.19%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 84 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
URETERITIS			
subjects affected / exposed	0 / 84 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION			
subjects affected / exposed	0 / 84 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
WOUND INFECTION			
subjects affected / exposed	0 / 84 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
DEHYDRATION			
subjects affected / exposed	0 / 84 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	CNI-Regimen	CNI-free-regimen	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	74 / 84 (88.10%)	65 / 78 (83.33%)	
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	9 / 84 (10.71%)	3 / 78 (3.85%)	
occurrences (all)	11	3	
General disorders and administration site conditions			
FATIGUE			
subjects affected / exposed	3 / 84 (3.57%)	4 / 78 (5.13%)	
occurrences (all)	4	4	
OEDEMA			
subjects affected / exposed	5 / 84 (5.95%)	2 / 78 (2.56%)	
occurrences (all)	5	2	
OEDEMA PERIPHERAL			
subjects affected / exposed	17 / 84 (20.24%)	20 / 78 (25.64%)	
occurrences (all)	21	21	
PYREXIA			
subjects affected / exposed	8 / 84 (9.52%)	5 / 78 (6.41%)	
occurrences (all)	11	5	
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	4 / 84 (4.76%)	5 / 78 (6.41%)	
occurrences (all)	6	6	
DYSPNOEA			
subjects affected / exposed	8 / 84 (9.52%)	5 / 78 (6.41%)	
occurrences (all)	10	5	
Investigations			
BLOOD CREATININE INCREASED			
subjects affected / exposed	5 / 84 (5.95%)	1 / 78 (1.28%)	
occurrences (all)	5	1	
C-REACTIVE PROTEIN INCREASED			
subjects affected / exposed	5 / 84 (5.95%)	3 / 78 (3.85%)	
occurrences (all)	5	3	

Cardiac disorders			
SINUS TACHYCARDIA			
subjects affected / exposed	3 / 84 (3.57%)	5 / 78 (6.41%)	
occurrences (all)	3	6	
TACHYCARDIA			
subjects affected / exposed	8 / 84 (9.52%)	7 / 78 (8.97%)	
occurrences (all)	9	7	
Nervous system disorders			
HEADACHE			
subjects affected / exposed	5 / 84 (5.95%)	7 / 78 (8.97%)	
occurrences (all)	6	9	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	6 / 84 (7.14%)	7 / 78 (8.97%)	
occurrences (all)	6	7	
LEUKOPENIA			
subjects affected / exposed	10 / 84 (11.90%)	10 / 78 (12.82%)	
occurrences (all)	11	13	
Gastrointestinal disorders			
APHTHOUS ULCER			
subjects affected / exposed	4 / 84 (4.76%)	5 / 78 (6.41%)	
occurrences (all)	4	5	
DIARRHOEA			
subjects affected / exposed	11 / 84 (13.10%)	5 / 78 (6.41%)	
occurrences (all)	11	6	
NAUSEA			
subjects affected / exposed	10 / 84 (11.90%)	6 / 78 (7.69%)	
occurrences (all)	10	7	
VOMITING			
subjects affected / exposed	5 / 84 (5.95%)	2 / 78 (2.56%)	
occurrences (all)	7	2	
Skin and subcutaneous tissue disorders			
ACNE			
subjects affected / exposed	3 / 84 (3.57%)	6 / 78 (7.69%)	
occurrences (all)	3	6	
RASH			

subjects affected / exposed	5 / 84 (5.95%)	2 / 78 (2.56%)	
occurrences (all)	6	2	
Endocrine disorders			
HYPERTHYROIDISM			
subjects affected / exposed	6 / 84 (7.14%)	4 / 78 (5.13%)	
occurrences (all)	6	4	
Musculoskeletal and connective tissue disorders			
MUSCLE SPASMS			
subjects affected / exposed	7 / 84 (8.33%)	1 / 78 (1.28%)	
occurrences (all)	7	1	
MYALGIA			
subjects affected / exposed	6 / 84 (7.14%)	1 / 78 (1.28%)	
occurrences (all)	6	1	
OSTEOPOROSIS			
subjects affected / exposed	2 / 84 (2.38%)	5 / 78 (6.41%)	
occurrences (all)	3	5	
PAIN IN EXTREMITY			
subjects affected / exposed	5 / 84 (5.95%)	1 / 78 (1.28%)	
occurrences (all)	5	1	
Infections and infestations			
BRONCHITIS			
subjects affected / exposed	8 / 84 (9.52%)	3 / 78 (3.85%)	
occurrences (all)	8	3	
CYTOMEGALOVIRUS INFECTION			
subjects affected / exposed	11 / 84 (13.10%)	4 / 78 (5.13%)	
occurrences (all)	14	4	
NASOPHARYNGITIS			
subjects affected / exposed	23 / 84 (27.38%)	12 / 78 (15.38%)	
occurrences (all)	35	15	
ORAL HERPES			
subjects affected / exposed	2 / 84 (2.38%)	5 / 78 (6.41%)	
occurrences (all)	2	5	
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 84 (1.19%)	4 / 78 (5.13%)	
occurrences (all)	1	5	
Metabolism and nutrition disorders			

HYPERCHOLESTEROLAEMIA			
subjects affected / exposed	7 / 84 (8.33%)	3 / 78 (3.85%)	
occurrences (all)	7	3	
HYPERLIPIDAEMIA			
subjects affected / exposed	9 / 84 (10.71%)	5 / 78 (6.41%)	
occurrences (all)	9	5	
HYPERTRIGLYCERIDAEMIA			
subjects affected / exposed	8 / 84 (9.52%)	6 / 78 (7.69%)	
occurrences (all)	8	6	
HYPERURICAEMIA			
subjects affected / exposed	5 / 84 (5.95%)	2 / 78 (2.56%)	
occurrences (all)	5	2	
HYPOKALAEMIA			
subjects affected / exposed	7 / 84 (8.33%)	13 / 78 (16.67%)	
occurrences (all)	7	13	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 April 2010	Amendment 1: Clarification of the involvement of a CRO
22 November 2012	Amendment 2: Clarification of exclusion criteria misunderstandings. Criteria missing from the synopsis or protocol text but mentioned in the corresponding part were completed The required time frames for SAE reporting were clarified. The study outline table was adapted to clearly indicate the timely application of medication.
22 January 2015	Amendment 3: The stopping rules for MPA were amended to clearly follow the recommendations given in a dear healthcare professional letter issued for CellCept® by Roche on 12-Dec-2014. This information was added to the sections Study drug administration, Permitted study drug adjustments, Premature patient withdrawal from study treatment, and Dose reduction of everolimus and MPA. Two exclusion criteria were amended for enhanced study feasibility in line with clinical praxis and patients' de facto condition: -Exclusion criterion 10 (enrollment) and exclusion criterion 4 (baseline) were modified to allow for inclusion of patients with leukocytes ≥ 3000/mm3 -Exclusion criterion 17 (enrollment) was removed.
25 November 2015	Amendment 4: Enrollment was to be terminated by 31-Dec-2015 due to slow recruitment and the inability to achieve the planned sample size in a considerable amount of time. At the time of preparation of this amendment, n = 160 patients had been randomized. A comment was added to Section 10.8. (Sample size calculation) In response to German Health Authority's request, the protocol was modified to implement most recent notifications for use of MPA based on the dear health care professional letter (DHCPL) that was sent out for CellCept® by Roche 10-Nov-2015. The novel safety information were added to section 6.5.1. (Study drug administration). Additional pregnancy β-hCG tests were implemented into section 7 (Visit schedule and assessments) and into the assessment schedule (Table 7-1) and are mandatory for all female patients of child bearing potential at screening, baseline, switch and every study visit.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported