



Clinical trial results:

Multicenter, Open-Label, Randomized, 24 Months Follow-up, Two Arm Study to Compare the Cardiovascular Profile in a Regimen With Everolimus + Mycophenolic Acid (MPA) Versus (vs.) a Regimen of CNI+MPA in Maintenance Renal Transplant Recipients (EVITA)

Summary

EudraCT number	2009-013780-19
Trial protocol	ES
Global end of trial date	03 March 2014

Results information

Result version number	v1 (current)
This version publication date	01 April 2016
First version publication date	01 April 2016

Trial information

Trial identification

Sponsor protocol code	CRAD001AES07
-----------------------	--------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01169701
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	03 March 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	03 March 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of the study was to compare the cardiovascular profile of an everolimus and mycophenolic acid immunosuppressive regimen with a calcineurin inhibitor and mycophenolic acid regimen in maintenance renal transplant 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. In addition, the patients' usual medications were administered throughout the study treatment period, until the final study assessments were completed. Medications necessary to treat infections, rejection episodes and adverse events were permitted but could require termination of the study medication. Concomitant medications which, according to their summary of product characteristics could interfere with tacrolimus (drug interactions) or everolimus, were avoided. In addition, the administration of therapies with medicinal products that potentiate the nephrotoxicity of tacrolimus (amphotericin B, ketoconazole, azapropazone and diclofenac) and therapies that interfere in the pharmacokinetics of tacrolimus, were avoided. All other immunosuppressive medicinal products that were not those specified in the protocol were not permitted, except those required to manage rejection episodes. Calcium channel blockers, or H2 receptor antagonists continuously, for up to four weeks prior to randomisation were accepted. Treatment with steroids was allowed according to the routine clinical practice of the site.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 August 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 71
Worldwide total number of subjects	71
EEA total number of subjects	71

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)	65
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This study was conducted at 9 kidney transplant centers in Spain. The enrolment of 80 maintenance renal transplant patients, between 18 and 70 years, who had had a first or second kidney transplant in the last 3 years was anticipated. Eighty patients were enrolled, of which 71 were included in the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Tacrolimus plus Mycophenolic Acid (MPA)

Arm description:

Patients continued with the same dose of tacrolimus+MPA as they were on prior to the start of the study (tacrolimus at levels of 4-7 ng/ml). Tacrolimus was administered as either Prograf® (twice a day) or Advagraf® (once daily in the morning) and could not be changed during the study. Mycophenolic acid (MPA) could be administered as Myfortic® (720-1440 mg/day or 360-1440 mg/day) or Cell-Sept® (1000-2000 mg/day or 500-2000 mg/day).

Arm type	Active comparator
Investigational medicinal product name	Tacrolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Patients in treatment with Prograf® took it twice a day and patients with Advagraf® once daily in the morning. In both cases, administration of the drug was performed in a consistent manner with respect to the time of day and meals. The capsules were administered on an empty stomach or at least 1 hour before, or 2 to 3 hours after the ingestion of food, to achieve maximum absorption.

Investigational medicinal product name	Mycophenolic Acid (MPA)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

MFS (Myfortic®): dose 720-1440 mg/day
MMF (Cell-Sept®): dose 1000-2000 mg/day

Although the following doses of MPA were permitted:

MFS (Myfortic®): dose 360-1440 mg/day
MMF (Cell-Sept®): dose 500-2000 mg/day

Arm title	Everolimus
------------------	------------

Arm description:

The investigational drug was everolimus (Certican®) for oral administration containing trough levels of 5-8 ng/ml, taken simultaneously with MPA every 12 hours. Tacrolimus was also administered and are detailed under dose and administration.

Arm type	Experimental
----------	--------------

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

Dosage and administration details:

Everolimus was taken twice daily simultaneously with MPA every 12 hours. Morning and evening doses were taken before, after or during meals according to the patient's choice and always in the same way. The starting dose (day 1) of everolimus with tacrolimus was 2 mg in the evening, maintaining full dose of Prograf® in the morning and reducing it to 50% in the evening. In the case of Advagraf®, 75% of the dose was administered in the morning. On Day 2 and 3, 2 mg of everolimus was administered in the morning and 2 mg in the evening, without tacrolimus. On Day 4-5 the everolimus trough levels were determined and adjusted between 5-8 ng/ml. The dose was adjusted by increasing the dose of everolimus if the trough level was less than 5 ng/ml and reducing the dose if the trough level was greater than 8 ng/ml. A follow-up trough level was performed on day 8 to ensure that the level was between 5-8 ng/ml. The same dose of MPA was continued as patient was on prior to starting the study.

Investigational medicinal product name	Tacrolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Patients in treatment with Prograf® took it twice a day and patients with Advagraf® once daily in the morning. In both cases, administration of the drug was performed in a consistent manner with respect to the time of day and meals. The capsules were administered on an empty stomach or at least 1 hour before, or 2 to 3 hours after the ingestion of food, to achieve maximum absorption.

Investigational medicinal product name	Mycophenolic Acid (MPA)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

MFS (Myfortic®): dose 720-1440 mg/day

MMF (Cell-Sept®): dose 1000-2000 mg/day

Although the following doses of MPA were permitted:

MFS (Myfortic®): dose 360-1440 mg/day

MMF (Cell-Sept®): dose 500-2000 mg/day

Number of subjects in period 1	Tacrolimus plus Mycophenolic Acid (MPA)	Everolimus
Started	36	35
Completed	31	25
Not completed	5	10
Consent withdrawn by subject	1	3
Adverse Event	1	2
Death	-	1
Administrative Problems	-	1
Sponsor Decision	-	1
Exclusion Criteria	2	-

Lost to follow-up	1	1
Serious Adverse Event	-	1

Baseline characteristics

Reporting groups

Reporting group title	Tacrolimus plus Mycophenolic Acid (MPA)
Reporting group description:	
Patients continued with the same dose of tacrolimus+MPA as they were on prior to the start of the study (tacrolimus at levels of 4-7 ng/ml). Tacrolimus was administered as either Prograf® (twice a day) or Advagraf® (once daily in the morning) and could not be changed during the study. Mycophenolic acid (MPA) could be administered as Myfortic® (720-1440 mg/day or 360-1440 mg/day) or Cell-Sept® (1000-2000 mg/day or 500-2000 mg/day).	
Reporting group title	Everolimus
Reporting group description:	
The investigational drug was everolimus (Certican®) for oral administration containing trough levels of 5-8 ng/ml, taken simultaneously with MPA every 12 hours. Tacrolimus was also administered and are detailed under dose and administration.	

Reporting group values	Tacrolimus plus Mycophenolic Acid (MPA)	Everolimus	Total
Number of subjects	36	35	71
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
arithmetic mean	49.1	47.4	
standard deviation	± 12	± 13.2	-
Gender categorical			
Units: Subjects			
Female	16	13	29
Male	20	22	42

End points

End points reporting groups

Reporting group title	Tacrolimus plus Mycophenolic Acid (MPA)
Reporting group description: Patients continued with the same dose of tacrolimus+MPA as they were on prior to the start of the study (tacrolimus at levels of 4-7 ng/ml). Tacrolimus was administered as either Prograf® (twice a day) or Advagraf® (once daily in the morning) and could not be changed during the study. Mycophenolic acid (MPA) could be administered as Myfortic® (720-1440 mg/day or 360-1440 mg/day) or Cell-Sept® (1000-2000 mg/day or 500-2000 mg/day).	
Reporting group title	Everolimus
Reporting group description: The investigational drug was everolimus (Certican®) for oral administration containing trough levels of 5-8 ng/ml, taken simultaneously with MPA every 12 hours. Tacrolimus was also administered and are detailed under dose and administration.	

Primary: Change from baseline in left ventricular mass index (LVMI)

End point title	Change from baseline in left ventricular mass index (LVMI)
End point description: Change from baseline in left ventricular hypertrophy (LVH) was assessed by echocardiogram where the left ventricular mass index was calculated. The presence of LVM was defined as $> 49.2 \text{ g/m}^{2.7}$ in men and $> 46.7 \text{ g/m}^{2.7}$ in women. A negative change from baseline indicates improvement. Analysis population included the Intent to Treat (ITT) analysis set, who had both baseline and month 24 values, were analyzed. The ITT included participants who received at least one dose of study medication and at least one post baseline LVMI value.	
End point type	Primary
End point timeframe: Baseline, Month 24	

End point values	Tacrolimus plus Mycophenolic Acid (MPA)	Everolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31 ^[1]	25 ^[2]		
Units: $\text{g/m}^{2.7}$				
arithmetic mean (standard deviation)				
Change from Baseline in LVMI	-6.071 (± 20.116)	-4.008 (± 17.61)		

Notes:

[1] - Intent to Treat (ITT) analysis set

[2] - Intent to Treat (ITT)

Statistical analyses

Statistical analysis title	LV Mass Index by Visit ITT Population-Tacrolimus
Statistical analysis description: LVMI was summarised by visit, presenting absolute values and changes with respect to the baseline value. An analysis of repeated measures was also conducted for the LVMI with treatment and the visit considered as fixed factors and LVMI baseline as covariate. The assessment of the primary endpoint was performed by means of the determination of the change in LVM between the visit at 24 months and the baseline visit, between the two treatment groups.	

Comparison groups	Tacrolimus plus Mycophenolic Acid (MPA) v Everolimus
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7753
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.45
upper limit	1.307
Variability estimate	Standard deviation

Statistical analysis title	LV Mass Index by Visit ITT Population-Everolimus
-----------------------------------	--

Statistical analysis description:

LVMi was summarised by visit, presenting absolute values and changes with respect to the baseline value. An analysis of repeated measures was also conducted for the LVMi with treatment and the visit considered as fixed factors and LVMi baseline as covariate. The assessment of the primary endpoint was performed by means of the determination of the change in LVM between the visit at 24 months and the baseline visit, between the two treatment groups.

Comparison groups	Everolimus v Tacrolimus plus Mycophenolic Acid (MPA)
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7753
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.28
upper limit	3.261
Variability estimate	Standard deviation

Secondary: Pulse Wave Velocity (PWV)

End point title	Pulse Wave Velocity (PWV)
-----------------	---------------------------

End point description:

Utilizing the SphygmoCor Device, ECG leads placed at the carotid and femoral arteries provided the measure of the pulse wave at that particular arterial location. The distance between the two vascular beds divided by the pulse wave time shift provided a measure of the pulse wave velocity. Participants from the safety analysis set were considered for this analysis. The safety analysis set included participants who received at least one dose of study medication. For each time point, only participants, who had values at both baseline and the given time point, were analyzed for that time point.

End point type	Secondary
----------------	-----------

End point timeframe:

Month 6, month 24

End point values	Tacrolimus plus Mycophenolic Acid (MPA)	Everolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36 ^[3]	35 ^[4]		
Units: m/sec				
arithmetic mean (standard deviation)				
Month 6 (n=31,30)	7.01 (± 1.62)	7.4 (± 1.62)		
Month 24 (n=28,25)	7.58 (± 1.68)	7.06 (± 1.74)		

Notes:

[3] - Safety Analysis Set

[4] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Major Cardiovascular Events (MACE)

End point title	Percentage of Participants with Major Cardiovascular Events (MACE)
-----------------	--

End point description:

A major cardiovascular event (MACE) included acute myocardial infarction, insertion or replacement of implantable defibrillator, peripheral vascular disorders, congestive heart failure, coronary artery bypass, other events, percutaneous coronary intervention, and stroke. This secondary endpoint examined the percentage of participants with MACE. This included the Intent to Treat (ITT) analysis set: The ITT included participants who received at least one dose of study medication and had at least one post baseline LVMI value.

End point type	Secondary
----------------	-----------

End point timeframe:

Month 24

End point values	Tacrolimus plus Mycophenolic Acid (MPA)	Everolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32 ^[5]	28 ^[6]		
Units: Percentatge of Participants				
number (not applicable)				
Percentage Participants with MACE	0	0		

Notes:

[5] - Intent to Treat Population. MACE=major cardiovascular event

[6] - Intent to Treat Population. MACE=major cardiovascular event

Statistical analyses

No statistical analyses for this end point

Secondary: Renal Function as Measured by Estimated Glomerular Filtration Rate

(eGFR)

End point title	Renal Function as Measured by Estimated Glomerular Filtration Rate (eGFR)
-----------------	---

End point description:

This secondary endpoint assesses renal function as measured by estimated glomerular filtration rate (eGFR). Estimated GFR was calculated using the modification of diet in renal disease (MDRD) formula. Participants from the safety analysis set were considered for this analysis. The safety analysis set included participants who received at least one dose of study medication. For each time point, only participants, who had values at both baseline and the given time point, were analyzed for that time point.

End point type	Secondary
----------------	-----------

End point timeframe:

Month 6, month 12, month 24

End point values	Tacrolimus plus Mycophenolic Acid (MPA)	Everolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36 ^[7]	35 ^[8]		
Units: mL /min/1.73 m ²				
arithmetic mean (standard deviation)				
Month 6 (n=33,29)	55.648 (± 11.244)	63.781 (± 18.38)		
Month 12 (n=32,28)	57.757 (± 11.391)	61.225 (± 19.239)		
Month 24 (n=31,26)	57.727 (± 10.498)	60.779 (± 17.023)		

Notes:

[7] - Safety Analysis Set

[8] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Biopsy-Proven Acute Rejection (BPAR), Graft Loss, Death, and Lost to Follow Up

End point title	Percentage of Participants with Biopsy-Proven Acute Rejection (BPAR), Graft Loss, Death, and Lost to Follow Up
-----------------	--

End point description:

The incidence of biopsy-proven acute rejection (BPAR), graft loss, death, and lost to follow-up events was calculated using relative frequency. The population analyzed was the Intent to Treat (ITT) population. The ITT included participants who received at least one dose of study medication and at least one post baseline LVMI value.

End point type	Secondary
----------------	-----------

End point timeframe:

Month 24

End point values	Tacrolimus plus Mycophenolic Acid (MPA)	Everolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32 ^[9]	28 ^[10]		
Units: Percentage of Participants				
number (not applicable)				
BPAR	0	0		
Graft Loss	0	0		
Deaths	0	0		
Lost to Follow-Up	3.13	0		

Notes:

[9] - Intent to Treat Population. BPAR=biopsy-proven acute rejection

[10] - Intent to Treat Population. BPAR=biopsy-proven acute rejection

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Cardiovascular Biomarkers: Troponin I and collagen type 1 C- telopeptide (ICTP)

End point title	Change from Baseline in Cardiovascular Biomarkers: Troponin I and collagen type 1 C- telopeptide (ICTP)
-----------------	---

End point description:

This secondary endpoint assesses change from baseline in cardiovascular biomarkers in both treatment arms. Blood samples were collected to analyze Troponin I and collagen type 1 C-telopeptide (ICTP). A negative change from baseline indicates improvement. Participants from the safety analysis set were considered for this analysis. The safety analysis set included participants who received at least one dose of study medication. For each time point, only participants, who had values at both baseline and the given time point, were analyzed for that time point.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline, month 6, month 24

End point values	Tacrolimus plus Mycophenolic Acid (MPA)	Everolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36 ^[11]	35 ^[12]		
Units: ng/ml				
arithmetic mean (standard deviation)				
Troponin 1, Month 6 (n=27,30)	0 (± 0.01)	-0.006 (± 0.026)		
Troponin 1, Month 24 (n=24,24)	0.003 (± 0.026)	-0.007 (± 0.018)		
ICTP, Month 6 (n=27,30)	0.049 (± 0.341)	-0.195 (± 0.234)		
ICTP, Month 24 (n=24,24)	-0.035 (± 0.366)	-0.125 (± 0.323)		

Notes:

[11] - Safety Analysis Set. ICTP=collagen type 1 C-telopeptide.

[12] - Safety Analysis Set. ICTP=collagen type 1 C-telopeptide.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean 24 hour Systolic and Diastolic Blood Bressure (Change from Baseline)

End point title	Mean 24 hour Systolic and Diastolic Blood Bressure (Change from Baseline)
-----------------	---

End point description:

Mean 24 hour systolic and diastolic blood pressure was measured using ambulatory blood pressure monitoring (ABPM). Participants from the safety analysis set were considered for this analysis. The safety analysis set included participants who received at least one dose of study medication. For each time point, only participants, who had values at both baseline and the given time point, were analyzed for that time point.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline, month 6, month 12, month 24

End point values	Tacrolimus plus Mycophenolic Acid (MPA)	Everolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31 ^[13]	30 ^[14]		
Units: mmHg				
arithmetic mean (standard deviation)				
Change from Baseline to Month 6 (n=31,29)	-0.6 (± 9.1)	3.2 (± 8.6)		
Change from Baseline to Month 12 (n=28,24)	2.1 (± 6.9)	2.7 (± 10.4)		
Change from Baseline to Month 24 (n=29,24)	2.2 (± 10.6)	2 (± 8.7)		

Notes:

[13] - Safety Analysis Set

[14] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Renal Function Measured by Serum Creatinine

End point title	Renal Function Measured by Serum Creatinine
-----------------	---

End point description:

Renal function was measured by serum creatinine. Serum samples were collected to analyze serum creatinine. Participants from the safety analysis set were considered for this analysis. The safety analysis set included participants who received at least one dose of study medication. For each time point, only participants, who had values at both baseline and the given time point, were analyzed for that time point.

End point type	Secondary
End point timeframe:	
Month 6, month 12, month 24	

End point values	Tacrolimus plus Mycophenolic Acid (MPA)	Everolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36 ^[15]	35 ^[16]		
Units: mg/dL				
arithmetic mean (standard deviation)				
Month 6 (n=33,29)	1.232 (± 0.272)	1.234 (± 0.36)		
Month 12 (n=32,28)	1.231 (± 0.278)	1.256 (± 0.367)		
Month 24 (n= 31,26)	1.217 (± 0.235)	1.26 (± 0.358)		

Notes:

[15] - Safety Analysis Set

[16] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Renal Function as Measured by Creatinine Clearance

End point title	Renal Function as Measured by Creatinine Clearance
-----------------	--

End point description:

Renal function was measured by creatinine clearance. Creatinine clearance was calculated using the Cockcroft-Gault formula. Participants from the safety analysis set were considered for this analysis. The safety analysis set included participants who received at least one dose of study medication. For each time point, only participants, who had values at both baseline and the given time point, were analyzed for that time point.

End point type	Secondary
End point timeframe:	
Month 6, month 12, month 24	

End point values	Tacrolimus plus Mycophenolic Acid (MPA)	Everolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36 ^[17]	35 ^[18]		
Units: mg/min				
arithmetic mean (standard deviation)				
Month 6 (n=29,25)	64.841 (± 16.163)	76.618 (± 27.708)		
Month 12 (n=28,25)	65.037 (± 15.866)	73.363 (± 25.989)		

Month 24 (n=28,24)	66.933 (\pm 13.264)	72.91 (\pm 23.926)		
--------------------	------------------------	-----------------------	--	--

Notes:

[17] - Safety Analysis Set

[18] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Cardiovascular Biomarker, Glycosylated Hemoglobin (HbA1c)

End point title	Change from Baseline in the Cardiovascular Biomarker, Glycosylated Hemoglobin (HbA1c)
-----------------	---

End point description:

Blood samples were collected to analyze HbA1c. A negative change from baseline indicates improvement. Participants from the safety analysis set were considered for this analysis. The safety analysis set included participants who received at least one dose of study medication. For each time point, only participants, who had values at both baseline and the given time point, were analyzed for that time point.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline, month 6, month 24

End point values	Tacrolimus plus Mycophenolic Acid (MPA)	Everolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36 ^[19]	35 ^[20]		
Units: Percentage of HbA1c				
arithmetic mean (standard deviation)				
Month 6 (n=20,22)	0.015 (\pm 0.184)	0.159 (\pm 0.346)		
Month 12 (n=22,20)	0.045 (\pm 0.237)	0.185 (\pm 0.407)		

Notes:

[19] - Safety Analysis Set.

[20] - Safety Analysis Set.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Cardiovascular Biomarker: Myeloperoxidase (MPO)

End point title	Change from Baseline in the Cardiovascular Biomarker: Myeloperoxidase (MPO)
-----------------	---

End point description:

Blood samples were collected to analyze myeloperoxidase (MPO). A negative change from baseline indicates improvement. Participants from the safety analysis set were considered for this analysis. The safety analysis set included participants who received at least one dose of study medication. For each time point, only participants, who had values at both baseline and the given time point, were analyzed for that time point.

End point type	Secondary
End point timeframe:	
Baseline, month 6, month 24	

End point values	Tacrolimus plus Mycophenolic Acid (MPA)	Everolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36 ^[21]	35 ^[22]		
Units: U/mL				
arithmetic mean (standard deviation)				
Month 6 (n=27,30)	0.433 (± 2.189)	-0.093 (± 1.158)		
Month 24 (n=24,24)	-0.329 (± 0.28)	-0.642 (± 0.972)		

Notes:

[21] - Safety Analysis Set

[22] - Safety Analysis Set.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Cardiovascular Biomarker, N-terminal Pro-brain Natriuretic Peptide Fraction (NT-proBNP)

End point title	Change from Baseline in the Cardiovascular Biomarker, N-terminal Pro-brain Natriuretic Peptide Fraction (NT-proBNP)
-----------------	---

End point description:

Blood samples were collected to analyze N-terminal pro-brain natriuretic peptide fraction (NT-proBNP). A negative change from baseline indicates improvement. Participants from the safety analysis set were considered for this analysis. The safety analysis set included participants who received at least one dose of study medication. For each time point, only participants, who had values at both baseline and the given time point, were analyzed for that time point.

End point type	Secondary
End point timeframe:	
Baseline, month 6, month 24	

End point values	Tacrolimus plus Mycophenolic Acid (MPA)	Everolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36 ^[23]	35 ^[24]		
Units: ng/mL				
arithmetic mean (standard deviation)				
Month 6 (n=27,30)	21.604 (± 294.82)	-79.1 (± 401.44)		
Month 24 (n=24,24)	-80.2 (± 424.24)	-193.3 (± 590.9)		

Notes:

[23] - Safety Analysis Set

[24] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Cardiovascular Biomarker, Type 1 Procollagen Amino-Terminal- Propeptide (PINP)

End point title	Change from Baseline in the Cardiovascular Biomarker, Type 1 Procollagen Amino-Terminal- Propeptide (PINP)
-----------------	--

End point description:

Blood samples were collected to analyze Type 1 procollagen amino-terminal- propeptide (PINP). A negative change from baseline indicates improvement. Participants from the safety analysis set were considered for this analysis. The safety analysis set included participants who received at least one dose of study medication. For each time point, only participants, who had values at both baseline and the given time point, were analyzed for that time point.

End point type	Secondary
End point timeframe:	
Baseline, month 6, month 24	

End point values	Tacrolimus plus Mycophenolic Acid (MPA)	Everolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36 ^[25]	35 ^[26]		
Units: ug/L				
arithmetic mean (standard deviation)				
Month 6 (n=27,30)	-13.82 (± 34.11)	-33.36 (± 33.227)		
Month 24 (n=24,24)	-13.65 (± 40.675)	-28.17 (± 30.381)		

Notes:

[25] - Safety Analysis Set

[26] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Cardiovascular Biomarkers, C-reactive Protein (CRP)

End point title	Change from Baseline in Cardiovascular Biomarkers, C-reactive Protein (CRP)
-----------------	---

End point description:

Blood samples were collected to analyze C-reactive protein (CRP). A negative change from baseline indicates improvement. Participants from the safety analysis set were considered for this analysis. The safety analysis set included participants who received at least one dose of study medication. For each

time point, only participants, who had values at both baseline and the given time point, were analyzed for that time point.

End point type	Secondary
End point timeframe:	
Baseline, month 6, month 24	

End point values	Tacrolimus plus Mycophenolic Acid (MPA)	Everolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36 ^[27]	35 ^[28]		
Units: mg/dL				
arithmetic mean (standard deviation)				
Month 6 (n=27,30)	0.512 (± 2.342)	0.326 (± 1.129)		
Month 24 (n=24,24)	0.1 (± 0.469)	-0.04 (± 1.683)		

Notes:

[27] - Safety Analysis Set

[28] - Safety Analysis Set

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 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	17.0
--------------------	------

Reporting groups

Reporting group title	Everolimus
-----------------------	------------

Reporting group description:

Everolimus

Reporting group title	Tacrolimus
-----------------------	------------

Reporting group description:

Tacrolimus

Serious adverse events	Everolimus	Tacrolimus	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 35 (22.86%)	5 / 36 (13.89%)	
number of deaths (all causes)	1	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	0 / 35 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system lymphoma			
subjects affected / exposed	0 / 35 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic neoplasm			

subjects affected / exposed	1 / 35 (2.86%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Surgical and medical procedures			
Arteriovenous fistula operation			
subjects affected / exposed	1 / 35 (2.86%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 35 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 35 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 35 (2.86%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 35 (2.86%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 35 (2.86%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			

subjects affected / exposed	1 / 35 (2.86%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	1 / 35 (2.86%)	0 / 36 (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			
Oral herpes			
subjects affected / exposed	1 / 35 (2.86%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 35 (2.86%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 35 (0.00%)	1 / 36 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			
subjects affected / exposed	1 / 35 (2.86%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 35 (2.86%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 35 (2.86%)	0 / 36 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Everolimus	Tacrolimus	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 35 (68.57%)	20 / 36 (55.56%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 35 (14.29%)	1 / 36 (2.78%)	
occurrences (all)	5	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 35 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Oedema peripheral			
subjects affected / exposed	6 / 35 (17.14%)	3 / 36 (8.33%)	
occurrences (all)	8	3	
Reproductive system and breast disorders			
Metrorrhagia			
subjects affected / exposed	2 / 35 (5.71%)	0 / 36 (0.00%)	
occurrences (all)	2	0	
Psychiatric disorders			
Depression			
subjects affected / exposed	2 / 35 (5.71%)	0 / 36 (0.00%)	
occurrences (all)	2	0	
Injury, poisoning and procedural complications			
Arteriovenous fistula site complication			
subjects affected / exposed	2 / 35 (5.71%)	0 / 36 (0.00%)	
occurrences (all)	3	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 35 (5.71%)	0 / 36 (0.00%)	
occurrences (all)	2	0	
Headache			
subjects affected / exposed	2 / 35 (5.71%)	2 / 36 (5.56%)	
occurrences (all)	2	3	
Blood and lymphatic system disorders			

Anaemia subjects affected / exposed occurrences (all)	3 / 35 (8.57%) 3	0 / 36 (0.00%) 0	
Leukopenia subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2	0 / 36 (0.00%) 0	
Polycythaemia subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2	1 / 36 (2.78%) 1	
Gastrointestinal disorders Aphthous stomatitis subjects affected / exposed occurrences (all)	3 / 35 (8.57%) 3	0 / 36 (0.00%) 0	
Diarrhoea subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 3	4 / 36 (11.11%) 4	
Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2	0 / 36 (0.00%) 0	
Dermatitis subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2	0 / 36 (0.00%) 0	
Seborrhoeic dermatitis subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	2 / 36 (5.56%) 3	
Renal and urinary disorders Proteinuria subjects affected / exposed occurrences (all)	5 / 35 (14.29%) 5	0 / 36 (0.00%) 0	
Musculoskeletal and connective tissue disorders Osteoporosis subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	2 / 36 (5.56%) 2	
Tendonitis			

subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	2 / 36 (5.56%) 2	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 35 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Nasopharyngitis			
subjects affected / exposed	2 / 35 (5.71%)	0 / 36 (0.00%)	
occurrences (all)	2	0	
Urinary tract infection			
subjects affected / exposed	0 / 35 (0.00%)	2 / 36 (5.56%)	
occurrences (all)	0	2	
Metabolism and nutrition disorders			
Dyslipidaemia			
subjects affected / exposed	1 / 35 (2.86%)	2 / 36 (5.56%)	
occurrences (all)	1	2	
Hypercalcaemia			
subjects affected / exposed	1 / 35 (2.86%)	3 / 36 (8.33%)	
occurrences (all)	1	3	
Hypercholesterolaemia			
subjects affected / exposed	2 / 35 (5.71%)	1 / 36 (2.78%)	
occurrences (all)	2	1	
Hyperglycaemia			
subjects affected / exposed	2 / 35 (5.71%)	2 / 36 (5.56%)	
occurrences (all)	2	2	
Hypertriglyceridaemia			
subjects affected / exposed	2 / 35 (5.71%)	0 / 36 (0.00%)	
occurrences (all)	2	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 March 2010	As a result of an exhaustive review with new participants, the exclusion criteria were extended in order to achieve a more defined study population.
30 April 2010	Changes in the study design (visit windows) were detected and included in this amendment.
28 June 2010	At the time of purchasing the study medication it was confirmed that not only was it necessary to supply the doses of 0.5 mg and 1 mg Certican but also the 0.25 mg dose. For this reason sections 4.3.1 and 4.4.1 of the protocol were changed.
02 February 2011	During the course of the study, it was verified that the determination of glycosylated haemoglobin (Hb1Ac) during the Glucose Tolerance Test (OGTT) at 2 hours was not relevant as changes are not appreciable until days or even months; thus it was decided to remove this measurement.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported