Clinical trial results:
Inmunosupresión óptima en pacientes con alto riesgo de diabetes de novo tras el trasplante renal: Un estudio prospectivo, multicéntrico, controlado y randomizado

Summary

EudraCT number	2008-005617-22
Trial protocol	ES
Global end of trial date	08 June 2015

Results information

Result version number	v1 (current)
This version publication date	30 October 2021
First version publication date	30 October 2021
Summary attachment (see zip file)	Publication of the trial (Clinical Trial_Article.pdf)

Trial information

Trial identification

Sponsor protocol code	01DMPT

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01002339
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Fundación Canaria Instituto de Investigación Sanitaria de Canarias (FIISC)
Sponsor organisation address	Bco Ballena s/n, Edificio Anexo Hospital Dr Negrin, Las Palmas de Gran Canaria, Spain, 35019
Public contact	Armando Torres Ramírez, Unidad de Investigación. Hospital Universitario de Canarias. Ofra s/n, 38320 La Laguna, Tenerife, 34 630989515, atorres@ull.edu.es
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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	23 December 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 February 2014
Global end of trial reached?	Yes
Global end of trial date	08 June 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Comparar la incidencia de diabetes de novo e intolerancia a la glucosa post-trasplante renal de un régimen inmunosupresor basado en Tacrolimus (Tacro) y supresión rápida de esteroides frente a Tacro o CsA con dosis reducidas de esteroides y supresión a los 6 meses, en pacientes con riesgo elevado de desarrollar DMPT.

Protection of trial subjects:

This is a Phase 4 RCT and all participants received standard of care to minimize pain and stress. In addition, a Contracted Insurance Policy was operative during the trial.

Background therapy:

Immunosuppressants apart from the calcineurin inhibitor (corticosteroids and mycophenolate mofetil); CMV prophylaxis (valganciclovir), Pneumocystis jirovecii prevention (cotrimoxazole), antihypertensives (RAS inhibitors), lipid-lowering drugs (statins).

Evidence for comparator:

Cyclosporine A (CsA) is less diabetogenic than Tacrolimus, specifically in renal transplant recipients at risk of post-transplant diabetes (older age, insulin resistance phenotype). In addition, early corticosteroid withdrawal has been shown to reduce the incidence of post-transplant diabetes in patients treated with Tacrolimus. We investigated whether CsA or Tacrolimus with rapid steroid withdrawal, are superior in terms of one-year post-transplant incidence of diabetes, than Tacrolimus and corticosteroid minimization.

Actual start date of recruitment	23 February 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 128
Worldwide total number of subjects	128
EEA total number of subjects	128

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	85
From 65 to 84 years	43
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Eight transplant centers in Spain participated in the study, which began on February 23, 2010. The Safety Committee decided to stop recruitment in the intermediate analysis but continue with the patients already recruited until the end of the study. Therefore, until February 5, 2014, a total of 128 patients were recruited.

Pre-assignment

Screening details:

-Assessed for eligibility(n = 211):
Scheduled delay of CNI initiationn = 51
Logistic problems n = 26

Randomized(n = 134)
Excluded: Error in the assigned study medication n = 1; Unjustified change of study medication n = 1; Randomized but not transplanted n = 1; Violation of I.C. n = 3

-Randomized and included (n = 128)

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Tac-SW

Arm description:

Tacrolimus-based immunosuppression and rapid steroid withdrawal (SW) within 1 week (Tac-SW)
Basiliximab induction. Tacrolimus plus Mycophenolate mofetil (MMF), and corticosteroids with rapid withdrawal after one week.

Arm type	Experimental
Investigational medicinal product name	Tacrolimus-based immunosuppresion and rapid steroid withdrawal
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet, Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Tac-SW arm: tacrolimus (Prograf) 0.15 mg/kg per day p.o. in 2 separate doses to maintain trough levels of 8 to 12 ng/ml in the first month, and mycophenolate mofetil (MMF; Cell Cept) 2 g/d p.o. Methyl-prednisolone 0.5 g i.v. intraoperatively and 125 mg on day 1; prednisone 30 mg p.o. on days 2 and 3, 20 mg on day 4, 15 mg on day 5, 10 mg on day 6, 5 mg on day 7, and then discontinuation.

Arm title	Tac-SM

Arm description:

Tacrolimus with steroids minimization (Tac-SM)
Basiliximab induction.Tacrolimus plus Mycophenolate mofetil (MMF) and low-dose corticosteroids for 6 months with subsequent removal

Arm type	Active comparator
Investigational medicinal product name	Tacrolimus with Steroid Minimization
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard, Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Tac-SM arm: tacrolimus and MMF following the same schedule as in arm 1. Intraoperative and day 1 methyl-prednisolone as in arm 1; prednisone 0.3 mg/kg per day p.o. from day 2 to 7 (never >20 mg/d), 0.2 mg/kg per day from day 8 to 14 (never >15 mg/d), 0.15 mg/kg per day from day 15 to 21 (never >10 mg/d), 0.1 mg/kg per day from day 22 to 28 (never >7.5 mg/d), and then 5 mg/d until 5 months, with subsequent gradual discontinuation over 4 weeks.

Arm title	CsA-SM

Arm description:

CsA with steroid minimization (CsA-SM)
Basiliximab induction. Ciclosporin A (CsA) plus Mycophenolate mofetil (MMF) and low-dose corticosteroids for 6 months with subsequent removal

Arm type	Experimental
Investigational medicinal product name	Cyclosporine A with Steroid Minimization
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft, Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

CsA-SM arm: Cyclosporine A microemulsion (Neoral) (CsA) 5 mg/kg per day p.o. to maintain C0 levels of 150–200 ng/ml the first month, and MMF and steroids following the same schedule as arm 2.

Investigational medicinal product name	Tacrolimus-based immunosuppresion and rapid steroid withdrawal
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard, Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Tac-SW arm: tacrolimus (Prograf) 0.15 mg/kg per day p.o. in 2 separate doses to maintain trough levels of 8 to 12 ng/ml in the first month, and mycophenolate mofetil (MMF; Cell Cept) 2 g/d p.o. Methyl-prednisolone 0.5 g i.v. intraoperatively and 125 mg on day 1; prednisone 30 mg p.o. on days 2 and 3, 20 mg on day 4, 15 mg on day 5, 10 mg on day 6, 5 mg on day 7, and then discontinuation.

Number of subjects in period 1	Tac-SW	Tac-SM	CsA-SM
Started	44	42	42
Completed	41	39	38
Not completed	3	3	4
Adverse event, serious fatal	2	1	2
Adverse event, non-fatal	1	2	2

Baseline characteristics

Reporting groups	
Reporting group title	Tac-SW
Reporting group description:	
Tacrolimus-based immunosuppression and rapid steroid withdrawal (SW) within 1 week (Tac-SW) Basiliximab induction. Tacrolimus plus Mycophenolate mofetil (MMF), and corticosteroids with rapid withdrawal after one week.	
Reporting group title	Tac-SM
Reporting group description:	
Tacrolimus with steroids minimization (Tac-SM) Basiliximab induction.Tacrolimus plus Mycophenolate mofetil (MMF) and low-dose corticosteroids for 6 months with subsequent removal	
Reporting group title	CsA-SM
Reporting group description:	
CsA with steroid minimization (CsA-SM) Basiliximab induction. Ciclosporin A (CsA) plus Mycophenolate mofetil (MMF) and low-dose corticosteroids for 6 months with subsequent removal	

Reporting group values	Tac-SW	Tac-SM	CsA-SM
Number of subjects	44	42	42
Age categorical			
There were no specific criteria for age in general. All patients from 18 years and over were eligible to participate. However, given the characteristics of renal disease, the participants were subject to the following metabolic inclusion and exclusion criteria inter alia: Age Inclusion Criteria: Recipient age >or =60 or Recipient age between 45 and 59 years and at least one of specific metabolic criteria defined in the criteria section study participants. Age Exclusion Criteria: Recipient age under 45 years.			
Units: Subjects			
18 years and over	44	42	42
Age continuous			
The Overall Number of Baseline Participants was a mean of 61.0 (7.7) years. Attending to the arm assigned mean age was: - Tacrolimus With Rapid Steroid Withdrawal: 61.2 (7.6) years. - Tacrolimus With Steroids Minimization: 61.6 (7.3) years. - CsA With Steroid Minimization: 60.2 (8.3) years.			
Units: years			
arithmetic mean	61.2	61.6	60.2
standard deviation	± 7.6	± 7.3	± 8.3
Gender categorical			
100% of Participants (128) of whom 27.34% (35) were female and 72.66% (93) were male. Attending to each arm, the average of each gender was: - Tac-SW : Female = 25.0% (11) Male= 75.0% (33) - Tac-SM : Female = 28.6% (12)			

Male= 71.4% (30)

- CsA-SM:
Female = 28.6% (12)
Male= 71.4% (30)

Units: Subjects			
Female	11	12	12
Male	33	30	30

Reporting group values	Total		
Number of subjects	128		
Age categorical			

There were no specific criteria for age in general. All patients from 18 years and over were eligible to participate. However, given the characteristics of renal disease, the participants were subject to the following metabolic inclusion and exclusion criteria inter alia:

Age Inclusion Criteria: Recipient age >or =60 or Recipient age between 45 and 59 years and at least one of specific metabolic criteria defined in the criteria section study participants.

Age Exclusion Criteria: Recipient age under 45 years.

Units: Subjects			
18 years and over	128		
Age continuous			

The Overall Number of Baseline Participants was a mean of 61.0 (7.7) years.

Attending to the arm assigned mean age was:

- Tacrolimus With Rapid Steroid Withdrawal: 61.2 (7.6) years.

- Tacrolimus With Steroids Minimization: 61.6 (7.3) years.

- CsA With Steroid Minimization: 60.2 (8.3) years.

Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			

100% of Participants (128) of whom 27.34% (35) were female and 72.66% (93) were male.

Attending to each arm, the average of each gender was:

- Tac-SW :
Female = 25.0% (11)
Male= 75.0% (33)

- Tac-SM :
Female = 28.6% (12)
Male= 71.4% (30)

- CsA-SM:
Female = 28.6% (12)
Male= 71.4% (30)

Units: Subjects			
Female	35		
Male	93		

End points

End points reporting groups

Reporting group title	Tac-SW
Reporting group description:	
Tacrolimus-based immunosuppression and rapid steroid withdrawal (SW) within 1 week (Tac-SW) Basiliximab induction. Tacrolimus plus Mycophenolate mofetil (MMF), and corticosteroids with rapid withdrawal after one week.	
Reporting group title	Tac-SM
Reporting group description:	
Tacrolimus with steroids minimization (Tac-SM) Basiliximab induction.Tacrolimus plus Mycophenolate mofetil (MMF) and low-dose corticosteroids for 6 months with subsequent removal	
Reporting group title	CsA-SM
Reporting group description:	
CsA with steroid minimization (CsA-SM) Basiliximab induction. Ciclosporin A (CsA) plus Mycophenolate mofetil (MMF) and low-dose corticosteroids for 6 months with subsequent removal	

Primary: New Onset Diabetes After Renal Transplantation

End point title	New Onset Diabetes After Renal Transplantation
End point description:	
American Diabetes Association criteria (ADA) including an oral glucose tolerance test.	
End point type	Primary
End point timeframe:	
1 year	

End point values	Tac-SW	Tac-SM	CsA-SM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	39	38	
Units: percentage of participants				
number (confidence interval 95%)	34.1 (21.6 to 49.5)	23.1 (12.7 to 38.3)	7.9 (2.7 to 20.8)	

Statistical analyses

Statistical analysis title	New Onset Diabetes After Renal Transplantation
Comparison groups	Tac-SW v Tac-SM v CsA-SM
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02
Method	Chi-squared

Primary: Patients Treated With Insulin or Oral Antidiabetic Drugs

End point title	Patients Treated With Insulin or Oral Antidiabetic Drugs

End point description:

End point type	Primary

End point timeframe:

1 year

End point values	Tac-SW	Tac-SM	CsA-SM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	39	38	
Units: percentage of participants				
number (confidence interval 95%)	20 (10.5 to 34.8)	15.4 (7.3 to 29.7)	2.6 (0.5 to 13.5)	

Statistical analyses

Statistical analysis title	Patients Treated With Insulin or Oral Antidiabetic
Comparison groups	Tac-SW v Tac-SM v CsA-SM
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.06
Method	Chi-squared

Primary: Primary Outcome Measure (Glucose Intolerance)

End point title	Primary Outcome Measure (Glucose Intolerance)

End point description:

Glycemia >=140 and <200 mg/dl, 2 hours after a standard oral glucose tolerance test. Measured values: glucose intolerance at 1 year defined by ADA criteria. Participants included are those that did not develop NODAT based on not reporting the use of antidiabetic drugs plus a fasting plasma glucose < 126 mg/dl.

End point type	Primary

End point timeframe:

1 year

End point values	Tac-SW	Tac-SM	CsA-SM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	26	29	30	
Units: percentage of participants				
number (confidence interval 95%)	26.9 (13.7 to 46.1)	31 (17.3 to 49.2)	33.3 (19.2 to 51.2)	

Statistical analyses

Statistical analysis title	Primary Outcome Measure (Glucose Intolerance)
Comparison groups	Tac-SW v Tac-SM v CsA-SM
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9
Method	Chi-squared

Secondary: Rejection

End point title	Rejection
End point description:	
Biopsy proven acute rejection. Measured variable: Rate of Biopsy proven acute rejection.	
End point type	Secondary
End point timeframe:	
1 year	

End point values	Tac-SW	Tac-SM	CsA-SM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	44	42	42	
Units: percentage of participants				
number (confidence interval 95%)	11.4 (4.95 to 24)	4.8 (1.3 to 15.8)	21.4 (11.7 to 36)	

Statistical analyses

Statistical analysis title	Rejection
Comparison groups	Tac-SW v Tac-SM v CsA-SM

Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.07
Method	Chi-squared

Secondary: Renal Function

End point title	Renal Function

End point description:

Estimated Glomerular Filtration Rate (ml/min/1.73 m^2)

End point type	Secondary

End point timeframe:

1 year

End point values	Tac-SW	Tac-SM	CsA-SM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	39	38	
Units: percentage of participants				
number (confidence interval 95%)	51.9 (45.2 to 58.5)	47.4 (42.9 to 52.0)	44.6 (37.8 to 51.3)	

Statistical analyses

Statistical analysis title	Renal Function
Comparison groups	Tac-SW v Tac-SM v CsA-SM
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2
Method	ANOVA

Secondary: Proteinuria

End point title	Proteinuria

End point description:

End point type	Secondary

End point timeframe:

1 year

End point values	Tac-SW	Tac-SM	CsA-SM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	39	36	36	
Units: mg/day				
number (confidence interval 95%)	208 (121 to 296)	241 (110 to 373)	343.2 (154 to 532)	

Statistical analyses

Statistical analysis title	Proteinuria
Statistical analysis description: Participants analyzed: participants living with a functioning graft at study end.	
Comparison groups	Tac-SW v Tac-SM v CsA-SM
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4
Method	ANOVA

Secondary: Blood Pressure

End point title	Blood Pressure
End point description: Systolic pressure (mmHg)	
End point type	Secondary
End point timeframe: 1 year	

End point values	Tac-SW	Tac-SM	CsA-SM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	39	39	36	
Units: mmHg				
arithmetic mean (standard deviation)	135.36 (± 15.75)	133.97 (± 13.67)	36 (± 17.27)	

Statistical analyses

Statistical analysis title	Blood Pressure
Comparison groups	Tac-SW v Tac-SM v CsA-SM
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8
Method	ANOVA

Secondary: Blood Pressure	
End point title	Blood Pressure
End point description: Diastolic pressure (mmHg)	
End point type	Secondary
End point timeframe: 1 year	

End point values	Tac-SW	Tac-SM	CsA-SM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	39	39	36	
Units: mmHg				
arithmetic mean (standard deviation)	76.67 (± 8.93)	74.59 (± 9.83)	76.64 (± 10.27)	

Statistical analyses

Statistical analysis title	Blood Pressure
Statistical analysis description: Diastolic pressure (mmHg)	
Comparison groups	Tac-SW v Tac-SM v CsA-SM
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.56
Method	ANOVA

Secondary: Number of Antihypertensive Drugs Patients Reported Taking.	
End point title	Number of Antihypertensive Drugs Patients Reported Taking.
End point description:	
End point type	Secondary

End point timeframe:

1 year

End point values	Tac-SW	Tac-SM	CsA-SM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	39	38	
Units: Number of Antihypertensive Drugs				
median (inter-quartile range (Q1-Q3))	2 (1 to 3)	2 (1 to 2)	2 (1 to 2)	

Statistical analyses

Statistical analysis title	Number of Antihypertensive Drugs Patients Reported
Comparison groups	Tac-SW v Tac-SM v CsA-SM
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8
Method	Kruskal-wallis

Secondary: Lipidic Profile (Triglycerides)

End point title	Lipidic Profile (Triglycerides)

End point description:

End point type	Secondary

End point timeframe:

1 year

End point values	Tac-SW	Tac-SM	CsA-SM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	39	37	37	
Units: mg/dl				
arithmetic mean (standard deviation)	159.44 (± 93.68)	145.59 (± 52.97)	160.78 (± 84.26)	

Statistical analyses

Statistical analysis title	Lipidic Profile (Triglycerides)
Comparison groups	Tac-SW v Tac-SM v CsA-SM
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.66
Method	ANOVA

Secondary: Lipidic Profile (Cholesterol)	
End point title	Lipidic Profile (Cholesterol)
End point description: Lipidic Profile (total cholesterol)	
End point type	Secondary
End point timeframe: 1 year	

End point values	Tac-SW	Tac-SM	CsA-SM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	39	37	38	
Units: mg/dl				
arithmetic mean (standard deviation)	169.05 (± 30.57)	178.24 (± 33.64)	168.89 (± 33.38)	

Statistical analyses

Statistical analysis title	Lipidic Profile (cholesterol)
Comparison groups	Tac-SW v Tac-SM v CsA-SM
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.37
Method	ANOVA

Secondary: Lipidic Profile (HDL-c)	
End point title	Lipidic Profile (HDL-c)
End point description:	
End point type	Secondary
End point timeframe: 1 year	

End point values	Tac-SW	Tac-SM	CsA-SM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	38	35	34	
Units: mg/dl				
arithmetic mean (standard deviation)	44.84 (± 13.89)	49.29 (± 16.90)	48.35 (± 16.59)	

Statistical analyses

Statistical analysis title	Lipidic Profile (HDL-c)
Comparison groups	Tac-SW v Tac-SM v CsA-SM
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.45
Method	ANOVA

Secondary: Lipidic Profile (LDL-c)

End point title	Lipidic Profile (LDL-c)

End point description:

End point type	Secondary

End point timeframe:

1 year

End point values	Tac-SW	Tac-SM	CsA-SM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37	35	34	
Units: mg/dl				
arithmetic mean (standard deviation)	94.00 (± 27.04)	95.43 (± 26.54)	88.65 (± 25.73)	

Statistical analyses

Statistical analysis title	Lipidic Profile (LDL-c)
Comparison groups	Tac-SW v Tac-SM v CsA-SM

Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5
Method	ANOVA

Secondary: Percentage of Patients Using Statins

End point title	Percentage of Patients Using Statins

End point description:

End point type	Secondary

End point timeframe:

1 year

End point values	Tac-SW	Tac-SM	CsA-SM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	39	38	
Units: percentage of participants				
number (confidence interval 95%)	56 (41 to 70)	61.5 (45.9 to 75.1)	73.7 (58 to 85)	

Statistical analyses

Statistical analysis title	Percentage of Patients Using Statins
Comparison groups	Tac-SW v Tac-SM v CsA-SM
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.17
Method	Chi-squared

Secondary: Changes of Carotid Intima-media Thickness Over Time

End point title	Changes of Carotid Intima-media Thickness Over Time

End point description:

The absolute difference between carotid intima-media thickness at study end versus baseline.

End point type	Secondary

End point timeframe:

1 year

End point values	Tac-SW	Tac-SM	CsA-SM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	8	10	
Units: mm				
arithmetic mean (confidence interval 95%)	0.12 (0.09 to 0.15)	0.04 (-0.15 to 0.23)	0.01 (-0.01 to 0.03)	

Statistical analyses

Statistical analysis title	Changes of Carotid Intima-media Thickness Over Tim
Comparison groups	Tac-SW v Tac-SM v CsA-SM
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5
Method	ANOVA

Secondary: Percentage of Patients Using Acetylsalicylic Acid (ASA)

End point title	Percentage of Patients Using Acetylsalicylic Acid (ASA)

End point description:

End point type	Secondary

End point timeframe:

1 year

End point values	Tac-SW	Tac-SM	CsA-SM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	39	37	36	
Units: percentage of participants				
number (confidence interval 95%)	53.9 (38.6 to 68.4)	48.7 (33.5 to 64.1)	52.8 (37 to 68)	

Statistical analyses

Statistical analysis title	Percentage of Patients Using Acetylsalicylic Acid
Comparison groups	Tac-SW v Tac-SM v CsA-SM

Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9
Method	Chi-squared

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Time frame, 1 year.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	2010

Reporting groups

Reporting group title	Tac-SW

Reporting group description:

Tacrolimus-based immunosuppression and rapid steroid withdrawal (SW) within 1 week (Tac-SW) Basiliximab induction. Tacrolimus plus Mycophenolate mofetil (MMF), and corticosteroids with rapid withdrawal after one week

Tacrolimus with rapid steroid withdrawal: Tacrolimus 0.15 mg/Kg/day to achieve target trough levels of 8-12 ng/ml for the first month, and MMF 2 gr/day; steroids: 0.5 gr of Methylprednisolone (MP) intraoperatively and 125 mg on the first day, followed by oral doses of prednisone rapidly tapered from 30 mg/day to complete discontinuation by postoperative day 7. Basiliximab induction (4 mg, days 0 and 4).

Reporting group title	Tac-SM

Reporting group description:

Tacrolimus with steroids minimization (Tac-SM)
Basiliximab induction.Tacrolimus plus Mycophenolate mofetil (MMF) and low-dose corticosteroids for 6 months with subsequent removal.

Tacrolimus with steroids minimization: Tacrolimus 0.15 mg/Kg/day to achieve target trough levels of 8-12 ng/ml for the first month, and MMF 2 gr/day; steroids: 0.5 gr of MP intraoperatively and 60 mg day 1; followed by oral doses of prednisone and gradual tapering to complete discontinuation over 6 months. Basiliximab induction (4 mg, days 0 and 4).

Reporting group title	CsA-SM

Reporting group description:

CsA with steroid minimization (CsA-SM)
Basiliximab induction. Ciclosporin A (CsA) plus Mycophenolate mofetil (MMF) and low-dose corticosteroids for 6 months with subsequent removal.

CsA with steroid minimization: CsA 5 mg/Kg/day to achieve target trough of 150-200 ng/ml the first month, and similar pattern with MMF and steroids as group 2. Basiliximab induction (4 mg, days 0 and 4).

Serious adverse events	Tac-SW	Tac-SM	CsA-SM
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 44 (18.18%)	5 / 42 (11.90%)	12 / 42 (28.57%)
number of deaths (all causes)	2	1	2
number of deaths resulting from adverse events	2	1	2
Cardiac disorders			
Heart Attack resulting in death event			

subjects affected / exposed	1 / 44 (2.27%)	0 / 42 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 8	0 / 5	0 / 12
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock resulting in death event			
subjects affected / exposed	0 / 44 (0.00%)	1 / 42 (2.38%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 8	1 / 5	0 / 12
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Immune system disorders			
Acute Rejection			
subjects affected / exposed	5 / 44 (11.36%)	2 / 42 (4.76%)	9 / 42 (21.43%)
occurrences causally related to treatment / all	5 / 8	2 / 5	9 / 12
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Graft Loss			
subjects affected / exposed	1 / 44 (2.27%)	2 / 42 (4.76%)	2 / 42 (4.76%)
occurrences causally related to treatment / all	1 / 8	2 / 5	2 / 12
deaths causally related to treatment / all	2 / 2	1 / 1	2 / 2
Infections and infestations			
Pneumonia resulting in death			
subjects affected / exposed	1 / 44 (2.27%)	0 / 42 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	1 / 8	0 / 5	1 / 12
deaths causally related to treatment / all	1 / 1	0 / 0	1 / 1
Sepsis resulting in death event			
subjects affected / exposed	0 / 44 (0.00%)	0 / 42 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 8	0 / 5	1 / 12
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Tac-SW	Tac-SM	CsA-SM
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 44 (27.27%)	17 / 42 (40.48%)	18 / 42 (42.86%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasia			

subjects affected / exposed	0 / 44 (0.00%)	1 / 42 (2.38%)	2 / 42 (4.76%)
occurrences (all)	12	17	18
Vascular disorders			
Stroke			
subjects affected / exposed	0 / 44 (0.00%)	1 / 42 (2.38%)	0 / 42 (0.00%)
occurrences (all)	12	17	18
Cardiac disorders			
Acute Miocardial Infarction or Coronary Revascularization			
subjects affected / exposed	0 / 44 (0.00%)	1 / 42 (2.38%)	2 / 42 (4.76%)
occurrences (all)	12	17	18
Infections and infestations			
Acute Pyelonephritis of the graft			
subjects affected / exposed	2 / 44 (4.55%)	6 / 42 (14.29%)	1 / 42 (2.38%)
occurrences (all)	12	17	18
BK Virus Infection			
subjects affected / exposed	4 / 44 (9.09%)	2 / 42 (4.76%)	3 / 42 (7.14%)
occurrences (all)	12	17	18
CMV Infection			
subjects affected / exposed	7 / 44 (15.91%)	6 / 42 (14.29%)	12 / 42 (28.57%)
occurrences (all)	12	17	18
Pneumonia			
subjects affected / exposed	0 / 44 (0.00%)	1 / 42 (2.38%)	1 / 42 (2.38%)
occurrences (all)	12	17	18
Sepsis			
subjects affected / exposed	1 / 44 (2.27%)	5 / 42 (11.90%)	1 / 42 (2.38%)
occurrences (all)	12	17	18

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
08 June 2014	The recruitment was prematurely stopped for safety reasons	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Mainly white population and of low immunological risk, make the results not representative of other transplant populations.

Donor-specific antibody data were not planned in the study designed and thus were not collected for patients with BPAR.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30450457