Clinical trial results:
AN OPEN, RANDOMISED, MULTICENTRE CLINICAL STUDY TO INVESTIGATE THE SAFETY AND EFFICACY OF STEROID WITHDRAWAL WITH TACROLIMUS, MYCOPHENOLATE MOFETIL AND DACLIZUMAB AGAINST TACROLIMUS, MYCOPHENOLATE MOFETIL AND STEROIDS IN CHILDREN AFTER KIDNEY TRANSPLANTATION

Summary

EudraCT number	2005-001348-22
Trial protocol	CZ GB SE HU BE DE IT
Global end of trial date	25 February 2008

Results information

Result version number	v1
This version publication date	04 May 2016
First version publication date	20 June 2015

Trial information

Trial identification

Sponsor protocol code	FG-506-02-43

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00296348
WHO universal trial number (UTN)	-
Other trial identifiers	International Study Number: PRG-EC-0243, Acronym: TWIST

Notes:

Sponsors

Sponsor organisation name	Astellas Pharma Europe Ltd
Sponsor organisation address	Lovett House, Lovett Road, Staines, United Kingdom, TW18 3AZ
Public contact	Clinical Trial Disclosure, Astellas Pharma Europe Ltd, Astellas.resultsdisclosure@astellas.com
Scientific contact	Clinical Trial Disclosure, Astellas Pharma Europe Ltd, Astellas.resultsdisclosure@astellas.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 February 2008
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 February 2008
Global end of trial reached?	Yes
Global end of trial date	25 February 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to investigate the impact of early corticosteroid withdrawal in paediatric renal transplant patients on growth expressed as change in height standard deviation score (SDS) from baseline to end of study (EOS).

Protection of trial subjects:

This clinical study was written, conducted and reported in accordance with the protocol, ICH GCP Guidelines, and applicable local regulations, including the European Directive 2001/20/EC, on the protection of human rights, and with the ethical principles that have their origin in the Declaration of Helsinki. Astellas ensures that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal, national and/or regional legislation related to the privacy and protection of personal information.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 September 2005
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	Sweden: 3
Country: Number of subjects enrolled	United Kingdom: 76
Country: Number of subjects enrolled	Belgium: 9
Country: Number of subjects enrolled	Czech Republic: 8
Country: Number of subjects enrolled	France: 17
Country: Number of subjects enrolled	Germany: 22
Country: Number of subjects enrolled	Hungary: 11
Country: Number of subjects enrolled	Italy: 14
Country: Number of subjects enrolled	Israel: 7
Country: Number of subjects enrolled	Poland: 23
Country: Number of subjects enrolled	Romania: 4
Country: Number of subjects enrolled	South Africa: 4
Country: Number of subjects enrolled	Taiwan: 2
Worldwide total number of subjects	200
EEA total number of subjects	187

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)	92
Adolescents (12-17 years)	108
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was performed in 32 centers across 13 countries.

Pre-assignment

Screening details:

Screening took place at baseline visit day 0. Screening assessments included: patient data, pregnancy test, donor/organ data, surgical details, body, height, weight, vital signs, blood pressure, and routine laboratory evaluations.

Period 1

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

Blinding implementation details:

This was an open label study so there was no blinding necessary.

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm 1: Tacrolimus+MMF+MAB(Daclizumab)+Corticosteroids(Day 0-4)

Arm description:

Arm 1 consisted of Tacrolimus, Mycophenolate mofetil (MMF), Daclizumab (MAB) and Corticosteriods as treatment for four days only.

Arm type	Experimental
Investigational medicinal product name	Tacrolimus
Investigational medicinal product code	FK506
Other name	Prograf
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Tacrolimus (both treatment arms): The initial daily dose was 0.3 mg/kg per os (oral) (p.o.) given in 2 doses (equals 0.15 mg/kg twice daily) post-operatively. The initial dose of 0.15 mg/kg of tacrolimus was to be administered within 12 hours after reperfusion. Recipients of a living donor organ could receive pre-dosing with tacrolimus according to the hospital’s routine practice. Subsequent oral tacrolimus doses would be adjusted based on clinical evidence of efficacy and occurrence of adverse events (AEs), and observing the following recommended tacrolimus whole blood trough level ranges: Day 0 -21: 10 - 20 ng/mL, Day 22 - 183: 5 - 15 ng/mL. Tacrolimus capsules were to be swallowed with fluid (preferably water, but not with grapefruit juice) at least 1 hour before meals or 2 hours after meals in the morning and in the evening. Administration of tacrolimus via nasogastric tube was allowed.

Investigational medicinal product name	Mycophenolate Mofetil
Investigational medicinal product code	
Other name	MMF
Pharmaceutical forms	Capsule, Powder for oral suspension
Routes of administration	Oral use

Dosage and administration details:

MMF (both treatment arms): The initial dose of 600 mg/m^2 of MMF was to be given pre-operatively. The first postoperative dose of MMF was administered within 12 hours following reperfusion. The daily dose was 1200 mg/m^2 given in 2 doses (equals 600 mg/m^2 twice daily) for the first 2 weeks. Thereafter a daily dose was 600 mg/m^2 given in 2 doses (equals 300 mg/m^2 twice daily). The total daily dose could be adjusted if medically indicated.

Investigational medicinal product name	Daclizumab
Investigational medicinal product code	
Other name	MAB

Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Daclizumab (used in treatment arm 1 only). The first dose of daclizumab of 1.0 mg/kg had to be administered intravenously within 24 hours before reperfusion. The second dose of daclizumab of 1.0 mg/kg had to be given intravenously on post-operative Day 14. Only 2 doses of daclizumab could be given. The calculated volume of daclizumab must be mixed with 50 mL of sterile 0.9% sodium chloride solution and administered via a central vein over a 15 minute period. When mixing the solution, it was not to be shaken, but gently inverted in order to avoid foaming. Care must be taken to assure sterility of the prepared solution because the drug product does not contain any antimicrobial preservatives or bacteriostatic agents.

Investigational medicinal product name	Corticosteroids
Investigational medicinal product code	
Other name	Methylprednisolone or equivalent
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous bolus use , Oral use

Dosage and administration details:

Corticosteroids were not provided as study medication but were administered as additional immunosuppressive treatment. Corticosteroids – for treatment arm 1:
Methylprednisolone or equivalent:
Day 0*: 300-600 mg/m^2 i.v. bolus followed by oral (*= pre-, intra-, or post-operatively)
Prednisone or equivalent:
Day 1: 60 mg/m^2 p.o.
Day 2: 40 mg/m^2 p.o.
Day 3: 30 mg/m^2 p.o.
Day 4: 20 mg/m^2 p.o.
Day 5- 183: none

Arm title	Arm 2: Tacrolimus + MMF + Corticosteroids

Arm description:

Arm 2 consisted of Tacrolimus, Mycophenolate mofetil (MMF) and Corticosteriods as treatment.

Arm type	Active comparator
Investigational medicinal product name	Tacrolimus
Investigational medicinal product code	FK506
Other name	Prograf
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Tacrolimus (both treatment arms): The initial daily dose was 0.3 mg/kg p.o. given in 2 doses (equals 0.15 mg/kg twice daily) post-operatively. The initial dose of 0.15 mg/kg of tacrolimus was to be administered within 12 hours after reperfusion. Recipients of a living donor organ could receive pre-dosing with tacrolimus according to the hospital’s routine practice. Subsequent oral tacrolimus doses would be adjusted based on clinical evidence of efficacy and occurrence of AEs, and observing the following recommended tacrolimus whole blood trough level ranges: Day 0 -21: 10 - 20 ng/mL, Day 22 - 183: 5 - 15 ng/mL. Tacrolimus capsules were to be swallowed with fluid (preferably water, but not with grapefruit juice) at least 1 hour before meals or 2 hours after meals in the morning and in the evening. Administration of tacrolimus via nasogastric tube was allowed.

Investigational medicinal product name	Mycophenolate Mofetil
Investigational medicinal product code	
Other name	MMF
Pharmaceutical forms	Capsule, Powder for oral suspension
Routes of administration	Oral use

Dosage and administration details:

MMF (both treatment arms): The initial dose of 600 mg/m^2 of MMF was to be given pre-operatively. The first postoperative dose of MMF was administered within 12 hours following reperfusion. The daily dose was 1200 mg/m^2 given in 2 doses (equals 600 mg/m^2 twice daily) for the first 2 weeks. Thereafter a daily dose was 600 mg/m^2 given in 2 doses (equals 300 mg/m^2 twice daily). The total daily dose could be adjusted if medically indicated.

Investigational medicinal product name	Corticosteroids
Investigational medicinal product code	
Other name	Methylprednisolone or equivalent
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous bolus use , Oral use

Dosage and administration details:

Corticosteroids were not provided as study medication but were administered as additional immunosuppressive treatment. Corticosteroids – for treatment arm 2:
Methylprednisolone or equivalent:
Day 0*: 300-600 mg/m^2 i.v. bolus followed by oral (*= pre, intra-, or post-op)
Prednisone or equivalent:
Day 1: 60 mg/m^2 p.o.
Day 2-7: 40 mg/m^2 p.o.
Day 8-14: 30 mg/m^2 p.o.
Day 15-28: 20 mg/m^2 p.o.
Day 29-42: 10 mg/m^2 p.o.
Day 43-183: < 10 mg/m^2 p.o.

Number of subjects in period 1	Arm 1: Tacrolimus+MMF+MAB(Daclizumab)+Corticosteroids(Day 0-4)	Arm 2: Tacrolimus + MMF + Corticosteroids
Started	100	100
Completed	85	84
Not completed	15	16
Administrative	-	3
Protocol violation	2	-
Adverse event	8	7
Investigator decision	1	-
Not transplanted	2	2
Inadaptation of galenic form	-	1
Lack of efficacy	2	3

Baseline characteristics

Reporting groups	
Reporting group title	Arm 1: Tacrolimus+MMF+MAB(Daclizumab)+Corticosteroids(Day 0-4)
Reporting group description:	
Arm 1 consisted of Tacrolimus, Mycophenolate mofetil (MMF), Daclizumab (MAB) and Corticosteriods as treatment for four days only.	
Reporting group title	Arm 2: Tacrolimus + MMF + Corticosteroids
Reporting group description:	
Arm 2 consisted of Tacrolimus, Mycophenolate mofetil (MMF) and Corticosteriods as treatment.	

Reporting group values	Arm 1: Tacrolimus+MMF+MAB(Daclizumab)+Corticosteroids(Day 0-4)	Arm 2: Tacrolimus + MMF + Corticosteroids	Total
Number of subjects	100	100	200
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			
Age values are based on the Full Analysis Set (FAS). The FAS contains all randomized and transplanted patients with results attributed to the treatment group that they were randomized to and who received at least one dose of study medication (tacrolimus, MMF, daclizumab or steroids).			
Units: years			
arithmetic mean	10.8	11.3	
standard deviation	± 4.2	± 4.1	-
Gender categorical			
Gender values are based on the FAS.			
Units: Subjects			
Female	32	39	71
Male	66	59	125
Subjects not included in FAS	2	2	4
Height			
Height values are based on the FAS.			
Units: cm			
arithmetic mean	134.4	136.8	
standard deviation	± 24.9	± 23.9	-

End points

End points reporting groups

Reporting group title	Arm 1: Tacrolimus+MMF+MAB(Daclizumab)+Corticosteroids(Day 0-4)

Reporting group description:

Arm 1 consisted of Tacrolimus, Mycophenolate mofetil (MMF), Daclizumab (MAB) and Corticosteriods as treatment for four days only.

Reporting group title	Arm 2: Tacrolimus + MMF + Corticosteroids

Reporting group description:

Arm 2 consisted of Tacrolimus, Mycophenolate mofetil (MMF) and Corticosteriods as treatment.

Primary: Growth, expressed as change in height Standard Deviation Score (SDS) from baseline to End of Study (EOS)

End point title	Growth, expressed as change in height Standard Deviation Score (SDS) from baseline to End of Study (EOS)

End point description:

The study analysis population for this endpoint consisted of the Primary Analysis Set (PAS). The PAS contains all randomized and transplanted patients who received at least one dose of study medication and who have valid measurements (i.e. excluding estimated values) of stature height at baseline and Month 6 (Visit 8 for completers, follow-up visit for withdrawn patients). Missing height at Visit 8 or at 6-month follow up (also for lost to follow-up patients) was estimated with the last available height (last observation carried forward (LOCF)). The change in height SDS from baseline will be calculated according to the formula:

Δ SDS = SDSEOS - SDSbaseline,
Where
SDS = (heightmeasured - heightstandard population)/SDstandard population.

The two treatment groups will be compared and tested for differences in mean change in height SDS from baseline.

End point type	Primary

End point timeframe:

Baseline to End of Study (EOS), up to 6 months.

End point values	Arm 1: Tacrolimus+MMF+MAB(Daclizumab)+Corticosteroids(Day 0-4)	Arm 2: Tacrolimus + MMF + Corticosteroids		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93	91		
Units: N/A (see SDS formula)				
arithmetic mean (standard deviation)	0.17 (± 0.4)	0.04 (± 0.3)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

The two treatment groups will be compared and tested for differences in mean change in height SDS from baseline. The null and alternative hypotheses are: H0: μST = μSF versus Ha: μST ≠ μSF, where μST and μSF represent the mean change in height SDS from baseline to EOS in the steroid treated group (ST) and the steroid free group (SF) respectively.

Comparison groups	Arm 1: Tacrolimus+MMF+MAB(Daclizumab)+Corticosteroids(Day 0-4)
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.005
Method	ANCOVA
Parameter estimate	Treatment group diff. in adj. mean ch.
Point estimate	0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.04
upper limit	0.23

Notes:

[1] - Parameter estimate: Treatment group difference in adjusted mean change. The primary endpoint was analyzed by ANCOVA with the factors treatment group, pubertal status and the covariate baseline height SDS on the primary analysis set.

Secondary: Number of participants with acute rejections (AR)

End point title	Number of participants with acute rejections (AR)

End point description:

FAS population. SRAR: not treated with new/increasing corticosteroids, antibodies/other meds and resolved regardless of tacrolimus/MMF dose changes. CSAR: treated with new/increased corticosteroids only and resolved, regardless of tacrolimus/MMF dose changes. A corticosteroid resistant acute rejection (CRAR) was defined as a rejection episode which did not resolve following treatment with corticosteroids. Rejection episodes which were initially treated with antibodies only were also be included in this category. Other acute rejection: could not be classified into the above categories. Chronic rejections were identified from biopsy findings and AE reporting during medical review.

End point type	Secondary

End point timeframe:

Up to 6 months.

End point values	Arm 1: Tacrolimus+MMF+MAB(Daclizumab)+Corticosteroids(Day 0-4)	Arm 2: Tacrolimus + MMF + Corticosteroids		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	98		
Units: Participants				
Acute rejections (AR)	20	16		
Spontaneously resolving acute rejections (SRAR)	1	0		
Corticosteroid sensitive acute rejections (CSAR)	18	14		

Corticosteroid resistant acute rejections (CRAR)	2	4		
Other rejections	0	0		
Chronic rejections	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with corticosteroid-resistant acute rejections (CRAR)

End point title	Number of participants with corticosteroid-resistant acute rejections (CRAR)

End point description:

The study analysis population for this endpoint consisted of the FAS. A corticosteroid resistant acute rejection (CRAR) was defined as a rejection episode which did not resolve following treatment with corticosteroids. Rejection episodes which were initially treated with antibodies only were also be included in this category.

End point type	Secondary

End point timeframe:

Up to 6 months.

End point values	Arm 1: Tacrolimus+MMF+MAB(Daclizumab)+Corticosteroids(Day 0-4)	Arm 2: Tacrolimus + MMF + Corticosteroids		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	98		
Units: Participants				
Corticosteroid resistant acute rejections (CRAR)	2	4		
Resolved with further treatment	1	3		
Unresolved with further treatment	1	0		
Unresolved without further treatment	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall AR episodes

End point title	Overall AR episodes

End point description:

The study analysis population for this endpoint consisted of the FAS.

End point type	Secondary

End point timeframe:

Up to 6 months.

End point values	Arm 1: Tacrolimus+MMF+MAB(Daclizumab)+Corticosteroids(Day 0-4)	Arm 2: Tacrolimus + MMF + Corticosteroids		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	98		
Units: AR episodes	24	21		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with biopsy-proven acute rejections (BPAR)

End point title	Number of participants with biopsy-proven acute rejections (BPAR)

End point description:

The study analysis population for this endpoint consisted of the FAS. An acute rejection episode was biopsy proven if one biopsy result between the start date and the stop date was classified as 'mild acute rejection (Banff I)', 'moderate acute rejection (Banff II)' or 'severe acute rejection (Banff III)'.

End point type	Secondary

End point timeframe:

Up to 6 months.

End point values	Arm 1: Tacrolimus+MMF+MAB(Daclizumab)+Corticosteroids(Day 0-4)	Arm 2: Tacrolimus + MMF + Corticosteroids		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	98		
Units: Participants				
Biopsy-proven acute rejections (BPAR)	10	7		
Biopsy-proven SRAR	0	0		
Biopsy-proven CSAR	9	5		
Biopsy-proven CRAR	1	3		
Other biopsy-proven rejections	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with biopsy-proven corticosteroid-resistant acute rejections (BCAR)

End point title	Number of participants with biopsy-proven corticosteroid-resistant acute rejections (BCAR)

End point description:

The study analysis population for this endpoint consisted of the FAS. An acute rejection episode was biopsy proven if one biopsy result between the start date and the stop date was classified as 'mild acute rejection (Banff I)', 'moderate acute rejection (Banff II)' or 'severe acute rejection (Banff III)'.

End point type	Secondary

End point timeframe:

Up to 6 months.

End point values	Arm 1: Tacrolimus+MMF+MAB(Daclizumab)+Corticosteroids(Day 0-4)	Arm 2: Tacrolimus + MMF + Corticosteroids		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	98		
Units: Participants				
Biopsy-proven corticosteroid-resistant AR (BCAR)	1	3		
Resolved with further treatment	1	3		
Unresolved with further treatment	0	0		
Unresolved without further treatment	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall BPAR episodes

End point title	Overall BPAR episodes

End point description:

The study analysis population for this endpoint consisted of the FAS.

End point type	Secondary

End point timeframe:

Up to 6 months.

End point values	Arm 1: Tacrolimus+MMF+MAB(Daclizumab)+Corticosteroids(Day 0-4)	Arm 2: Tacrolimus + MMF + Corticosteroids		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	98		
Units: BPAR episodes	13	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Severity of BPARs

End point title	Severity of BPARs

End point description:

The study analysis population for this endpoint consisted of the FAS. The histological evaluation of biopsies for the grade of acute rejections were based on the Banff 97 working classification of renal allograft pathology.

End point type	Secondary

End point timeframe:

Up to 6 months.

End point values	Arm 1: Tacrolimus+MMF+MAB(Daclizumab)+Corticosteroids(Day 0-4)	Arm 2: Tacrolimus + MMF + Corticosteroids		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	98		
Units: Biopsies				
No rejection	43	24		
Mild AR (Banff I)	10	6		
Moderate AR (Banff II)	2	3		
Severe AR (Banff III)	1	1		
Other	28	17		
Total	84	51		

Statistical analyses

No statistical analyses for this end point

Secondary: Patient survival

End point title	Patient survival

End point description:

The study analysis population for this endpoint consisted of the FAS. Event and censor times for the Kaplan-Meier analyses of patient survival: day of death, day of last follow-up for withdrawn patients and day of last visit for completers and lost to follow-up.

End point type	Secondary

End point timeframe:

Up to 6 months.

End point values	Arm 1: Tacrolimus+MMF+MAB(Daclizumab)+Corticosteroids(Day 0-4)	Arm 2: Tacrolimus + MMF + Corticosteroids		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	98		
Units: Percentage				
number (confidence interval 95%)	99 (97 to 100)	100 (100 to 100)		

Statistical analyses

No statistical analyses for this end point

Secondary: Graft survival

End point title	Graft survival

End point description:

The study analysis population for this endpoint consisted of the FAS. Event and censor times for the Kaplan-Meier analyses of graft survival: day of graft loss, day of last follow-up for withdrawn patients and day of last visit for completers and lost to follow-up. Graft loss is defined as retransplantation, nephrectomy or death or as dialysis ongoing at study end or withdrawal of the patient from the study unless superseded by follow up information.

End point type	Secondary

End point timeframe:

Up to 6 months

End point values	Arm 1: Tacrolimus+MMF+MAB(Daclizumab)+Corticosteroids(Day 0-4)	Arm 2: Tacrolimus + MMF + Corticosteroids		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	98		
Units: Percentage				
number (confidence interval 95%)	96.9 (93.5 to 100)	96.9 (93.5 to 100)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with adverse events (AEs)

End point title	Number of participants with adverse events (AEs)

End point description:

The study analysis population for this endpoint consisted of the FAS. An adverse event (AE) was defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with treatment. The obligation to report AEs starts with the enrolment of a patient in the study.

End point type	Secondary

End point timeframe:

Up to 6 months.

End point values	Arm 1: Tacrolimus+MMF+MAB(Daclizumab)+Corticosteroids(Day 0-4)	Arm 2: Tacrolimus + MMF + Corticosteroids		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	98		
Units: Participants				
Adverse Events	95	93		
Serious Adverse Events (SAEs)	63	60		
Causally-related adverse events	76	79		
Causally-related serious adverse events	43	37		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in serum lipids

End point title	Absolute change in serum lipids

End point description:

The study analysis population for this endpoint consisted of the FAS.

End point type	Secondary

End point timeframe:

Change from visit 1/baseline to visit 8/day 183 (up to 6 months).

End point values	Arm 1: Tacrolimus+MMF+MAB(Daclizumab)+Corticosteroids(Day 0-4)	Arm 2: Tacrolimus + MMF + Corticosteroids		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	98		
Units: mmol/L				
arithmetic mean (standard deviation)				
Total Cholesterol [N= 72, 74]	-0.94 (± 1.666)	-0.42 (± 1.213)		
LDL [N= 49, 56]	-0.21 (± 0.863)	-0.3 (± 0.998)		
HDL [N= 56, 62]	0.04 (± 0.31)	0.05 (± 0.357)		
Triglycerides [N= 68, 72]	-1.14 (± 1.803)	-0.42 (± 1.174)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with delayed graft function (DGF)

End point title	Number of participants with delayed graft function (DGF)

End point description:

Delayed graft function is defined as post-operative dialysis for more than one day during the time period from Day 0 to Day 7. Never functioning graft is defined as dialysis from the first week on until study end or withdrawal, unless a functioning graft was reported at follow-up.

End point type	Secondary

End point timeframe:

Up to day 7 (week 1), DGF must be within 7 days of transplant .

End point values	Arm 1: Tacrolimus+MMF+MAB(Daclizumab)+Corticosteroids(Day 0-4)	Arm 2: Tacrolimus + MMF + Corticosteroids		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	98		
Units: Participants	9	11		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of DGF

End point title	Duration of DGF

End point description:

The study analysis population for this endpoint consisted of the FAS.

End point type	Secondary

End point timeframe:

Up to day 7 (week 1), DGF must be within 7 days of transplant .

End point values	Arm 1: Tacrolimus+MMF+MAB(Daclizumab)+Corticosteroids(Day 0-4)	Arm 2: Tacrolimus + MMF + Corticosteroids		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	98		
Units: Dialysis days				
median (full range (min-max))	8 (3 to 18)	4 (1 to 23)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with renal dysfunction

End point title	Number of participants with renal dysfunction

End point description:

The study analysis population for this endpoint consisted of the FAS. Renal dysfunction is defined as GFR < 40 mL/min/1.73m^2 (Schwartz formula) at Visit 8 (Month 6).

End point type	Secondary

End point timeframe:

Up to 6 months.

End point values	Arm 1: Tacrolimus+MMF+MAB(Daclizumab)+Corticosteroids(Day 0-4)	Arm 2: Tacrolimus + MMF + Corticosteroids		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	98		
Units: Participants	7	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with post transplantation diabetes mellitus (PTDM)

End point title	Number of participants with post transplantation diabetes mellitus (PTDM)
End point description:	
The study analysis population for this endpoint consisted of the FAS.	
End point type	Secondary
End point timeframe:	
Up to 6 months.	

End point values	Arm 1: Tacrolimus+MMF+MAB(Daclizumab)+Corticosteroids(Day 0-4)	Arm 2: Tacrolimus + MMF + Corticosteroids		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	98		
Units: Participants	0	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with hypertension

End point title	Number of participants with hypertension
End point description:	
The study analysis population for this endpoint consisted of the FAS.	
End point type	Secondary
End point timeframe:	
Up to 6 months.	

End point values	Arm 1: Tacrolimus+MMF+MAB(Daclizumab)+Corticosteroids(Day 0-4)	Arm 2: Tacrolimus + MMF + Corticosteroids		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	98		
Units: Participants	21	25		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first AR

End point title	Time to first AR

End point description:

The study analysis population for this endpoint consisted of subjects with AR. Time to first acute rejection episode was defined as the number of days from reperfusion to the first clinical, laboratory or histological signs that were considered to be related to the first acute rejection episode.

End point type	Secondary

End point timeframe:

Up to 6 months.

End point values	Arm 1: Tacrolimus+MMF+MAB(Daclizumab)+Corticosteroids(Day 0-4)	Arm 2: Tacrolimus + MMF + Corticosteroids		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	16		
Units: Days				
median (full range (min-max))	35 (3 to 147)	24 (2 to 116)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first CRAR

End point title	Time to first CRAR

End point description:

The study analysis population for this endpoint consisted of subjects with CRAR. Time to first corticosteroid resistant acute rejection episode was defined as the number of days from reperfusion to the first clinical, laboratory or histological signs that were considered to be related to the first CRAR episode.

End point type	Secondary

End point timeframe:

Up to 6 months.

End point values	Arm 1: Tacrolimus+MMF+MAB(Daclizumab)+Corticosteroids(Day 0-4)	Arm 2: Tacrolimus + MMF + Corticosteroids		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	4		
Units: Days				
median (full range (min-max))	52.5 (9 to 96)	43.5 (2 to 109)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first BPAR

End point title	Time to first BPAR

End point description:

The study analysis population for this endpoint consisted of subjects with BPAR. Time to first biopsy-proven acute rejection episode was defined as the number of days from reperfusion to the first clinical, laboratory or histological signs that were considered to be related to the first BPAR episode.

End point type	Secondary

End point timeframe:

Up to 6 months.

End point values	Arm 1: Tacrolimus+MMF+MAB(Daclizumab)+Corticosteroids(Day 0-4)	Arm 2: Tacrolimus + MMF + Corticosteroids		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	7		
Units: Days				
median (full range (min-max))	26.5 (3 to 147)	34 (2 to 116)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first BCAR

End point title	Time to first BCAR

End point description:

The study analysis population for this endpoint consisted of subjects with BCAR. Time to first biopsy-proven corticosteroid-resistant
acute rejection episode was defined as the number of days from reperfusion to the first clinical, laboratory or histological signs that were considered to be related to the first BCAR episode.

End point type	Secondary

End point timeframe:

Up to 6 months.

End point values	Arm 1: Tacrolimus+MMF+MAB(Daclizumab)+Corticosteroids(Day 0-4)	Arm 2: Tacrolimus + MMF + Corticosteroids		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	3		
Units: Days				
median (full range (min-max))	9 (9 to 9)	10 (2 to 77)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

An adverse event was considered treatment-emergent if it started on or after the day of first study medication intake(tacrolimus, MMF, MAB or steroids).

Adverse event reporting additional description:

FAS population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	8.0

Reporting groups

Reporting group title	Tacrolimus + MMF + MAB (Daclizumab) + Corticosteroids

Reporting group description:

This arm consisted of Tacrolimus, Mycophenolate mofetil (MMF), Daclizumab (MAB) and Corticosteriods as treatment.

Reporting group title	Tacrolimus + MMF + Corticosteroids

Reporting group description:

This arm consisted of Tacrolimus, Mycophenolate mofetil (MMF) and Corticosteriods as treatment.

Serious adverse events	Tacrolimus + MMF + MAB (Daclizumab) + Corticosteroids	Tacrolimus + MMF + Corticosteroids	
Total subjects affected by serious adverse events			
subjects affected / exposed	63 / 98 (64.29%)	60 / 98 (61.22%)	
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)			
Lymphoproliferative disorder			
subjects affected / exposed	2 / 98 (2.04%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			

subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphocele			
subjects affected / exposed	1 / 98 (1.02%)	3 / 98 (3.06%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Medical device removal			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrostomy			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stent placement			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
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			
Asthenia			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Implant site effusion			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (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			
Anaphylactic reaction			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft loss			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound complication			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal stenosis			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	2 / 98 (2.04%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatinine increased			

subjects affected / exposed	17 / 98 (17.35%)	7 / 98 (7.14%)	
occurrences causally related to treatment / all	11 / 20	6 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glucose tolerance decreased			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immunosuppressant drug level decreased			
subjects affected / exposed	1 / 98 (1.02%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Arteriovenous fistula thrombosis			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clavicle fracture			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complications of transplant surgery			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complications of transplanted kidney			

subjects affected / exposed	2 / 98 (2.04%)	2 / 98 (2.04%)	
occurrences causally related to treatment / all	1 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft haemorrhage			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft thrombosis			
subjects affected / exposed	1 / 98 (1.02%)	2 / 98 (2.04%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Operative haemorrhage			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative respiratory distress			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stent occlusion			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular procedure complication			

subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (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			
Convulsion			
subjects affected / exposed	1 / 98 (1.02%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertonia			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 98 (1.02%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow depression			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolytic uraemic syndrome			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Leukopenia			
subjects affected / exposed	1 / 98 (1.02%)	2 / 98 (2.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	3 / 98 (3.06%)	2 / 98 (2.04%)	
occurrences causally related to treatment / all	2 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis haemorrhagic			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	1 / 98 (1.02%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peptic ulcer			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	3 / 98 (3.06%)	2 / 98 (2.04%)	
occurrences causally related to treatment / all	0 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Bladder obstruction			
subjects affected / exposed	2 / 98 (2.04%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysuria			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glomerulonephritis proliferative			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			

subjects affected / exposed	1 / 98 (1.02%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	5 / 98 (5.10%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	2 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertonic bladder			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrocalcinosis			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephropathy			
subjects affected / exposed	2 / 98 (2.04%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephropathy toxic			
subjects affected / exposed	8 / 98 (8.16%)	2 / 98 (2.04%)	
occurrences causally related to treatment / all	8 / 8	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrotic syndrome			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proteinuria			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal artery thrombosis			

subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (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	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal tubular necrosis			
subjects affected / exposed	4 / 98 (4.08%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	2 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal vein thrombosis			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric obstruction			
subjects affected / exposed	1 / 98 (1.02%)	3 / 98 (3.06%)	
occurrences causally related to treatment / all	1 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric stenosis			
subjects affected / exposed	2 / 98 (2.04%)	2 / 98 (2.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract disorder			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vesicoureteric reflux			

subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Rhabdomyolysis			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenovirus infection			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BK virus infection			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (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 / 98 (1.02%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial pyelonephritis			
subjects affected / exposed	2 / 98 (2.04%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis viral			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Catheter bacteraemia			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium colitis			
subjects affected / exposed	1 / 98 (1.02%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			
subjects affected / exposed	5 / 98 (5.10%)	10 / 98 (10.20%)	
occurrences causally related to treatment / all	3 / 5	8 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dental caries			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epstein-Barr virus infection			
subjects affected / exposed	2 / 98 (2.04%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema infectiosum			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection			
subjects affected / exposed	2 / 98 (2.04%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			

subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis clostridial			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis rotavirus			
subjects affected / exposed	2 / 98 (2.04%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	3 / 98 (3.06%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	3 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gingival infection			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis infectious mononucleosis			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes simplex			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral candidiasis			

subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis bacterial			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis bacterial			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngotonsillitis			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (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 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	1 / 98 (1.02%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection bacterial			

subjects affected / exposed	3 / 98 (3.06%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection viral			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	2 / 98 (2.04%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection bacterial			
subjects affected / exposed	1 / 98 (1.02%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			
subjects affected / exposed	6 / 98 (6.12%)	3 / 98 (3.06%)	
occurrences causally related to treatment / all	4 / 7	4 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection enterococcal			

subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection fungal			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection pseudomonal			
subjects affected / exposed	2 / 98 (2.04%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral diarrhoea			
subjects affected / exposed	2 / 98 (2.04%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	2 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	3 / 98 (3.06%)	3 / 98 (3.06%)	
occurrences causally related to treatment / all	1 / 3	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 98 (1.02%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			

subjects affected / exposed	0 / 98 (0.00%)	4 / 98 (4.08%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus insulin-dependent			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid intake reduced			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glucose tolerance impaired			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercholesterolaemia			
subjects affected / exposed	0 / 98 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypervolaemia			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (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	Tacrolimus + MMF + MAB (Daclizumab) + Corticosteroids	Tacrolimus + MMF + Corticosteroids	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	79 / 98 (80.61%)	82 / 98 (83.67%)	
Investigations			
Blood creatinine increased			
subjects affected / exposed	17 / 98 (17.35%)	12 / 98 (12.24%)	
occurrences (all)	24	15	
Blood pressure increased			
subjects affected / exposed	6 / 98 (6.12%)	3 / 98 (3.06%)	
occurrences (all)	6	3	
Injury, poisoning and procedural complications			
Complications of transplanted kidney			
subjects affected / exposed	6 / 98 (6.12%)	9 / 98 (9.18%)	
occurrences (all)	6	9	
Vascular disorders			
Hypertension			
subjects affected / exposed	21 / 98 (21.43%)	25 / 98 (25.51%)	
occurrences (all)	21	25	
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 98 (5.10%)	5 / 98 (5.10%)	
occurrences (all)	7	8	
Tremor			
subjects affected / exposed	4 / 98 (4.08%)	8 / 98 (8.16%)	
occurrences (all)	5	10	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	22 / 98 (22.45%)	7 / 98 (7.14%)	
occurrences (all)	23	7	
Leukopenia			
subjects affected / exposed	5 / 98 (5.10%)	1 / 98 (1.02%)	
occurrences (all)	5	1	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	8 / 98 (8.16%)	6 / 98 (6.12%)	
occurrences (all)	12	6	

Pyrexia			
subjects affected / exposed	5 / 98 (5.10%)	2 / 98 (2.04%)	
occurrences (all)	5	2	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 98 (1.02%)	6 / 98 (6.12%)	
occurrences (all)	1	6	
Abdominal pain			
subjects affected / exposed	7 / 98 (7.14%)	5 / 98 (5.10%)	
occurrences (all)	7	5	
Diarrhoea			
subjects affected / exposed	22 / 98 (22.45%)	20 / 98 (20.41%)	
occurrences (all)	27	29	
Nausea			
subjects affected / exposed	8 / 98 (8.16%)	3 / 98 (3.06%)	
occurrences (all)	11	3	
Vomiting			
subjects affected / exposed	12 / 98 (12.24%)	6 / 98 (6.12%)	
occurrences (all)	13	7	
Renal and urinary disorders			
Nephropathy toxic			
subjects affected / exposed	6 / 98 (6.12%)	0 / 98 (0.00%)	
occurrences (all)	6	0	
Renal tubular necrosis			
subjects affected / exposed	5 / 98 (5.10%)	3 / 98 (3.06%)	
occurrences (all)	5	3	
Infections and infestations			
Cytomegalovirus infection			
subjects affected / exposed	7 / 98 (7.14%)	5 / 98 (5.10%)	
occurrences (all)	8	5	
Epstein-Barr virus infection			
subjects affected / exposed	5 / 98 (5.10%)	3 / 98 (3.06%)	
occurrences (all)	7	3	
Febrile infection			
subjects affected / exposed	7 / 98 (7.14%)	0 / 98 (0.00%)	
occurrences (all)	9	0	
Respiratory tract infection			

subjects affected / exposed	1 / 98 (1.02%)	5 / 98 (5.10%)	
occurrences (all)	1	5	
Respiratory tract infection viral			
subjects affected / exposed	6 / 98 (6.12%)	2 / 98 (2.04%)	
occurrences (all)	9	2	
Rhinitis			
subjects affected / exposed	5 / 98 (5.10%)	1 / 98 (1.02%)	
occurrences (all)	8	1	
Urinary tract infection bacterial			
subjects affected / exposed	13 / 98 (13.27%)	12 / 98 (12.24%)	
occurrences (all)	18	23	
Viral upper respiratory tract infection			
subjects affected / exposed	3 / 98 (3.06%)	7 / 98 (7.14%)	
occurrences (all)	3	10	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	3 / 98 (3.06%)	12 / 98 (12.24%)	
occurrences (all)	4	14	
Hypokalaemia			
subjects affected / exposed	2 / 98 (2.04%)	6 / 98 (6.12%)	
occurrences (all)	2	6	
Hypomagnesaemia			
subjects affected / exposed	2 / 98 (2.04%)	6 / 98 (6.12%)	
occurrences (all)	2	6	
Hypophosphataemia			
subjects affected / exposed	2 / 98 (2.04%)	8 / 98 (8.16%)	
occurrences (all)	2	8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 February 2006	Amendment 2, a substantial amendment, (dated 20 February, 2006) allowed for the introduction of 2 sub-studies within this study; one for the study "Estimation of Rejection Risk in Kidney Recipients by Novel Immunological Markers" and one for study "Pharmacokinetics and Pharmacogenetics of tacrolimus and MMF". These 2 sub-studies were performed only at trial sites which agreed to participate in the additional tests and obtained an approval by the responsible Ethics Committee and Competent Authority where applicable. These sub-studies and the obtained data do not form a part of the clinical report for study FG-506-02-43.
17 July 2006	Amendment 3, a substantial amendment, (dated 17 July, 2006) made the change that body height and weight were not to be measured at Visit 2 (Day 1 after operation), since children, unlike adults, are usually not mobilized on the day of surgery. This change did not jeopardize evaluation of study results since the main endpoint of the study compared patient height at baseline (before surgery) to that at the end of study (at 6 months after surgery).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/25539467