Clinical trial results:
A MULTICENTER, TWO ARM, RANDOMIZED, OPEN LABEL CLINICAL STUDY INVESTIGATING RENAL FUNCTION IN AN ADVAGRAF®-BASED IMMUNOSUPPRESSIVE REGIMEN WITH OR WITHOUT SIROLIMUS IN KIDNEY TRANSPLANT SUBJECTS

Summary

EudraCT number	2010-019639-37
Trial protocol	CZ AT DE ES SK NL IT BE
Global end of trial date	18 September 2013

Results information

Result version number	v1 (current)
This version publication date	01 April 2016
First version publication date	22 May 2015

Trial information

Trial identification

Sponsor protocol code	PMR-EC-1212

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01363752
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Astellas Pharma Europe Ltd.
Sponsor organisation address	2000 Hillswood Drive, Chertsey, Surrey, United Kingdom, KT16 0RS
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	18 September 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 September 2013
Global end of trial reached?	Yes
Global end of trial date	18 September 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to compare the effect of 2 immunosuppressive therapy regimens on glomerular filtration rate (GFR) estimated by iohexol clearance at week 52 post kidney transplantation.

Arm 1: Advagraf + MMF + steroids
Arm 2: Advagraf + MMF (withdrawn at day 28) + steroids + sirolimus (introduced at day 28) in combination with reduced Advagraf dose at day 42 (week 6) to achieve lower tacrolimus target levels.

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 and/or regional legislation related to the privacy and protection of personal information.

Background therapy:

Advagraf®, MMF (CellCept®) and sirolimus (Rapamune®) were defined as study drugs in this study. Advagraf® and sirolimus were considered to be Investigational Medicinal Product (IMP) and were provided by the Sponsor. MMF and iohexol although not considered to be IMP in this study were also provided by the Sponsor. Corticosteroids were also not considered to be IMP and were not provided by the Sponsor. All subjects took Advagraf, MMF and Steroids prior to transplant and randomization. Advagraf Day 0 – Day 27 Pre-operative dose 0.1 mg/ kg was given orally in one dose, at any time within 12 hours prior to reperfusion and if possible within 3 hours prior to anesthesia. The initial post-operative dose is 0.2 mg/ kg/ day given orally in one dose, preferably in the morning and should not be administered less than 4 hours after pre-operative dose or more than 12 hours after reperfusion. Advagraf® doses were adjusted on the basis of clinical evidence of efficacy and occurrence of AEs and observing the following recommended whole blood trough level ranges: Day 0 – 14: 10 – 15 ng/ ml, Day 15 – 27: 8 – 12 ng/ ml. MMF Day 0 - Day 27. A loading dose of 1g of MMF was given preoperatively. First post-operative dose of MMF was administered within 24 hours following reperfusion. The daily dose of 2g (3g/ day for Black or African-American subjects) was given orally and split into two dose (equals 1g twice daily) for the first 14 days. Thereafter the daily dose is reduced to 1g given in two doses (equals 0.5g twice daily) until Day 28 (Visit 5). Corticosteroids IV (bolus) & oral, Methylprednisolone or equivalent Day 0: 0 – 1000 mg IV bolus (pre, intra, or post-op), Prednisolone or equivalent taken orally Day 1 – 13: 20 mg/ day, Day 14 – 28: 15 mg/ day.

Evidence for comparator:

Not applicable, this was an open label study.

Actual start date of recruitment	08 March 2011
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	Poland: 34
Country: Number of subjects enrolled	Netherlands: 27
Country: Number of subjects enrolled	Spain: 52
Country: Number of subjects enrolled	Austria: 48
Country: Number of subjects enrolled	Belgium: 15
Country: Number of subjects enrolled	Czech Republic: 13
Country: Number of subjects enrolled	France: 140
Country: Number of subjects enrolled	Germany: 154
Country: Number of subjects enrolled	Hungary: 25
Country: Number of subjects enrolled	Italy: 80
Country: Number of subjects enrolled	Australia: 2
Country: Number of subjects enrolled	Belarus: 46
Country: Number of subjects enrolled	Hong Kong: 6
Country: Number of subjects enrolled	Korea, Republic of: 33
Country: Number of subjects enrolled	Russian Federation: 37
Country: Number of subjects enrolled	Taiwan: 3
Country: Number of subjects enrolled	Turkey: 15
Worldwide total number of subjects	730
EEA total number of subjects	588

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	641
From 65 to 84 years	89
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This multicenter study was conducted at 58 sites in 18 European and Asia-Pacific countries.

Pre-assignment

Screening details:

Eligibility took place baseline/Visit 1, up to 96 hours prior to transplantation Day 0-Day 27 prior to randomization on Day 28/Visit 5. Screening assessments: pregnancy test, donor/organ data, surgical details, vital signs, height, weight, laboratory assessments, dispensing/collecting study drugs, serum creatinine/glucose and EQ-5D questionnaires.

Pre-assignment period milestones

Number of subjects started	853[1]
Number of subjects completed	730

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Not fulfilling inclusion/exclusion criteria: 13
Reason: Number of subjects	Retransplantation/graft loss: 5
Reason: Number of subjects	No study pre-treatment taken: 3
Reason: Number of subjects	Adverse event: 53
Reason: Number of subjects	Withdrawal of consent: 14
Reason: Number of subjects	Protocol violation: 7
Reason: Number of subjects	Miscellaneous: 28

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The Pre-assignment period "started" number reflects all subjects consented/enrolled. The Pre-assignment period "completed" number reflects all subjects that transplanted and randomized. The worldwide number includes all randomized subjects. Randomization for this study did not occur until transplantation Day 28/Visit 5.

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:

Not applicable, this was an open label study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Advagraf + MMF + Steroids

Arm description:

Arm 1 served as the reference arm for the study; the combination of tacrolimus and MMF has a proven efficacy and safety profile.

Arm type	Active comparator

Investigational medicinal product name	Advagraf
Investigational medicinal product code	FK506E (MR4)
Other name	prolonged release tacrolimus
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Advagraf® was defined as study drug in this study, considered to be Investigational Medicinal Product (IMP) and was provided by the Sponsor. Advagraf was available as hard gelatin capsules with 0.5 mg, 1 mg, 3 mg. For patients randomized to treatment Arm 1, the Advagraf daily dose continued to be administered orally once a day in the morning Day 28 to Day 365. The dosing was adjusted on the basis of clinical evidence of efficacy and occurrence of AEs and observing the following recommended blood trough levels: Days 28 through 41: 8 to 12 ng/mL, Days 42 through 365: 6 to 10 ng/mL. In the event that the patient was unable to swallow the Advagraf capsule, administration was permitted via nasogastric tube, as for normal oral administration of intact Advagraf capsules.

Investigational medicinal product name	Mycophenolate Mofetil
Investigational medicinal product code	
Other name	MMF, Cellcept
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

MMF (CellCept®) was defined as study drug in this study, although not considered to be IMP in this study it was provided by the Sponsor. CellCept was available as hard gelatin capsules with 250 mg MMF. MMF (Arm 1) Day 28 to Day 365, for patients randomized to treatment Arm 1, the MMF daily dose of 1 g was administered in 2 doses (equals 0.5 g twice daily) until the end-of-study (EOS) visit (visit 10).

Investigational medicinal product name	Corticosteroids
Investigational medicinal product code	
Other name	Steroids
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Corticosteroids were not provided by the Sponsor and were not considered to be investigational medicinal products (IMPs). Corticosteroids were a permitted concomitant immunosuppressive treatment. Prednisolone, or equivalent, orally was to be administered post randomization as follows: Day 29 through 42: 10 mg/day, Day 43 through 60: 5 mg/day, Day 60 through 365: ≤ 5 mg/day.

Arm title	Advagraf + MMF + Steroids + Sirolimus

Arm description:

Arm 2 Advagraf + MMF(withdrawn on Day 28) + Steroids + Sirolimus(introduced on Day 28) in combination with lower tacrolimus exposure at Day 42 (week 6) was compared to Arm 1.

Arm type	Experimental
Investigational medicinal product name	Advagraf
Investigational medicinal product code	FK506E (MR4)
Other name	prolonged release tacrolimus
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Advagraf® was defined as study drug in this study, considered to be Investigational Medicinal Product (IMP) and was provided by the Sponsor. Advagraf was available as hard gelatin capsules with 0.5 mg, 1 mg, 3 mg. For patients randomized to treatment Arm 2, Advagraf daily dose continued to be administered orally once a day in the morning through day 28 with dosing adjusted based on the following tacrolimus blood trough concentrations: Day 28 through 41: 8 to 12 ng/mL. Only for patients in Arm 2, the Advagraf dose was decreased by at least 25% to the following reduced target tacrolimus trough levels on day 42 (week 6): Day 42 through 365: 4 to 5 ng/mL. In the event that the patient was unable to swallow the Advagraf capsule, administration was permitted via nasogastric tube.

Investigational medicinal product name	Mycophenolate Mofetil
Investigational medicinal product code	
Other name	MMF, Cellcept
Pharmaceutical forms	Capsule, hard

Routes of administration	Oral use

Dosage and administration details:

MMF (CellCept®) was defined as study drug in this study, although not considered to be IMP in this study it was provided by the Sponsor. CellCept was available as hard gelatin capsules with 250 mg MMF. MMF dose was 1 g, given in 2 doses (equals 0.5 g twice daily), for patients randomized to treatment Arm 2, MMF was stopped on day 28 (visit 5) randomization day.

Investigational medicinal product name	Corticosteroids
Investigational medicinal product code	
Other name	Steroids
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Corticosteroids were not provided by the Sponsor and were not considered to be investigational medicinal products (IMPs). Corticosteroids were a permitted concomitant immunosuppressive treatment. Prednisolone, or equivalent, orally was to be administered post randomization as follows: Day 29 through 42: 10 mg/day, Day 43 through 60: 5 mg/day, Day 60 through 365: ≤ 5 mg/day.

Investigational medicinal product name	Sirolimus
Investigational medicinal product code	
Other name	Rapamune
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Sirolimus (Rapamune®) was available as 1 mg or 0.5 mg tablets. For patients randomized to treatment Arm 2, sirolimus was administered on days 28 through 365. Sirolimus initial daily doses of 1 mg were administered orally once a day in the morning. After the initial dosing subsequent sirolimus doses were taken orally once a day only in the morning and doses could be adjusted up to a maximum dose of 2 mg on the basis of clinical evidence of efficacy and occurrence of AEs and observing the following recommended whole blood trough level range: Day 28 through 365: 2 to 4 ng/mL.

Number of subjects in period 1	Advagraf + MMF + Steroids	Advagraf + MMF + Steroids + Sirolimus
Started	362	368
Completed	324	301
Not completed	38	67
Retransplantation/graft loss	2	2
Protocol violation	1	3
Miscellaneous	5	3
Adverse event	19	53
Not fulfilling inclusion/exclusion criteria	1	-
Withdrawal of consent	7	4
Lost to follow-up	3	2

Baseline characteristics

Reporting groups	
Reporting group title	Advagraf + MMF + Steroids
Reporting group description:	
Arm 1 served as the reference arm for the study; the combination of tacrolimus and MMF has a proven efficacy and safety profile.	
Reporting group title	Advagraf + MMF + Steroids + Sirolimus
Reporting group description:	
Arm 2 Advagraf + MMF(withdrawn on Day 28) + Steroids + Sirolimus(introduced on Day 28) in combination with lower tacrolimus exposure at Day 42 (week 6) was compared to Arm 1.	

Reporting group values	Advagraf + MMF + Steroids	Advagraf + MMF + Steroids + Sirolimus	Total
Number of subjects	362	368	730
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 provided are for the Intent-to-treat (ITT) population. The ITT population consisted of patients who had been transplanted (underwent reperfusion) and randomized.			
Units: years			
arithmetic mean	49.44	49.74	
standard deviation	± 13.065	± 13.11	-
Gender categorical			
Gender values provided are for the ITT population, the ITT population consisted of patients who had been transplanted (underwent reperfusion) and randomized.			
Units: Subjects			
Female	128	121	249
Male	234	247	481

End points

End points reporting groups

Reporting group title	Advagraf + MMF + Steroids
Reporting group description:	
Arm 1 served as the reference arm for the study; the combination of tacrolimus and MMF has a proven efficacy and safety profile.	
Reporting group title	Advagraf + MMF + Steroids + Sirolimus
Reporting group description:	
Arm 2 Advagraf + MMF(withdrawn on Day 28) + Steroids + Sirolimus(introduced on Day 28) in combination with lower tacrolimus exposure at Day 42 (week 6) was compared to Arm 1.	

Primary: Glomerular filtration rate (GFR) estimated by iohexol clearance at week 52 post kidney transplantation

End point title	Glomerular filtration rate (GFR) estimated by iohexol clearance at week 52 post kidney transplantation
End point description:	
Determination of GFR by iohexol clearance was obtained for each patient by performing regression analysis of the natural logarithm (iohexol plasma concentration) on sample time points, calculating the AUC, obtaining the iohexol clearance, and estimating the GFR from iohexol using Brochner-Mortensen correction. Patients who had graft loss (death, retransplantation or dialysis ongoing at study end or discontinuation) were included with a GFR of zero (0). Study analysis population for this endpoint consisted of the Full Analysis Set (FAS) population. The FAS population included patients who had been transplanted, randomized, and had a post-randomization assessment of the primary endpoint (that is, evaluable iohexol sample measurements). Missing end of treatment variables were imputed by last observation carried forward (LOCF).	
End point type	Primary
End point timeframe:	
End of Study (EOS), Week 52	

End point values	Advagraf + MMF + Steroids	Advagraf + MMF + Steroids + Sirolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	287	282		
Units: GFR by iohexol clearance mL/min/1.73 m2				
arithmetic mean (standard deviation)	45.48 (± 18.018)	46.37 (± 20.304)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
The hypothesis being tested for the primary variable is described as follows: H0: Mean iohexol clearance ARM 1 = Mean iohexol clearance rate ARM 2 H1: Mean iohexol clearance ARM 1 ≠ Mean iohexol clearance rate ARM 2	

Comparison groups	Advagraf + MMF + Steroids + Sirolimus v Advagraf + MMF + Steroids
Number of subjects included in analysis	569
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.405
Method	ANCOVA
Parameter estimate	Least-squares mean difference Arm2-Arm1
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.392
upper limit	3.441

Notes:

[1] - Analysis of Covariance (ANCOVA) model. The P value is from an ANCOVA model in which treatment arm, sex, race (Black or non-Black), site and donor status (deceased or nondeceased) were included as factors, estimated glomerular filtration rate (eGFR) Modification Diet in Renal Disease (4-variable) (MDRD4) at randomization and donor age are included as continuous covariates.

Secondary: Renal function at week 52 after transplantation assessed by GFR with the MDRD4

End point title	Renal function at week 52 after transplantation assessed by GFR with the MDRD4

End point description:

The study analysis population for this endpoint consisted of the FAS population. Patients who had graft loss (death, re-transplantation or dialysis ongoing at study end or discontinuation) were included with a GFR of 0.

End point type	Secondary

End point timeframe:

Up to week 52.

End point values	Advagraf + MMF + Steroids	Advagraf + MMF + Steroids + Sirolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	287	282		
Units: mL/min/1.73 m2				
arithmetic mean (standard deviation)	54.54 (± 20.388)	55.42 (± 23.368)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Advagraf + MMF + Steroids v Advagraf + MMF + Steroids + Sirolimus

Number of subjects included in analysis	569
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.72
Method	ANCOVA
Parameter estimate	Least-squares mean difference Arm2-Arm1
Point estimate	0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.213
upper limit	3.202

Notes:

[2] - Analysis of Covariance (ANCOVA) model. The P value is from an ANCOVA model in which treatment arm, sex, race (Black or non-Black), site and donor status (deceased or nondeceased) were included as factors, eGFR MDRD4 at randomization and donor age are included as continuous covariates.

Secondary: Renal function at week 52 after transplantation assessed by calculated creatinine clearance using the Cockcroft-Gault formula

End point title	Renal function at week 52 after transplantation assessed by calculated creatinine clearance using the Cockcroft-Gault formula

End point description:

The study analysis population for this endpoint consisted of the FAS population. Patients who had graft loss (death, re-transplantation or dialysis ongoing at study end or discontinuation) were included with a GFR of 0.

End point type	Secondary

End point timeframe:

Up to week 52.

End point values	Advagraf + MMF + Steroids	Advagraf + MMF + Steroids + Sirolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	287	282		
Units: mL/min				
arithmetic mean (standard deviation)	65.03 (± 26.761)	66.12 (± 27.868)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Advagraf + MMF + Steroids v Advagraf + MMF + Steroids + Sirolimus

Number of subjects included in analysis	569
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.736
Method	ANCOVA
Parameter estimate	Least-squares mean difference Arm2-Arm1
Point estimate	0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.541
upper limit	3.594

Notes:

[3] - Analysis of Covariance (ANCOVA) model. The P value is from an ANCOVA model in which treatment arm, sex, race (Black or non-Black), site and donor status (deceased or nondeceased) were included as factors, eGFR MDRD4 at randomization and donor age are included as continuous covariates.

Secondary: Renal function at week 52 after transplantation assessed by creatinine clearance with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula

End point title	Renal function at week 52 after transplantation assessed by creatinine clearance with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula

End point description:

The study analysis population for this endpoint consisted of the FAS population. Patients who had graft loss (death, re-transplantation or dialysis ongoing at study end or discontinuation) were included with a GFR of 0.

End point type	Secondary

End point timeframe:

Up to week 52.

End point values	Advagraf + MMF + Steroids	Advagraf + MMF + Steroids + Sirolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	287	282		
Units: mL/min/1.73m²				
arithmetic mean (standard deviation)	56 (± 21.935)	56.6 (± 24.242)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Advagraf + MMF + Steroids v Advagraf + MMF + Steroids + Sirolimus

Number of subjects included in analysis	569
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.823
Method	ANCOVA
Parameter estimate	Least-squares mean difference Arm2-Arm1
Point estimate	0.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.44
upper limit	3.066

Notes:

[4] - Analysis of Covariance (ANCOVA) model. The P value is from an ANCOVA model in which treatment arm, sex, race (Black or non-Black), site and donor status (deceased or nondeceased) were included as factors, eGFR MDRD4 at randomization and donor age are included as continuous covariates.

Secondary: Efficacy failure

End point title	Efficacy failure

End point description:

Efficacy failure defined as a composite endpoint consisting of any of the following: Graft Loss (retransplantation, nephrectomy, death or dialysis ongoing at the study end or at time of discontinuation from the study, unless superseded by follow-up information) or patient withdrawal. The study analysis population for this endpoint consisted of the ITT set. Patients with no events were censored at the date of last follow-up evaluation or date of death for patients who died or date of graft loss for patients with graft loss. Estimated Kaplan-Meier rates percentages at week 52 have been provided for efficacy failure.

End point type	Secondary

End point timeframe:

Up to week 52.

End point values	Advagraf + MMF + Steroids	Advagraf + MMF + Steroids + Sirolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	362	368		
Units: Percentage				
number (not applicable)	11.5	18.2		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Kaplan-Meier survival estimates (percentage) for the rate of patients with the event (Arm 2 minus Arm 1).

Comparison groups	Advagraf + MMF + Steroids + Sirolimus v Advagraf + MMF + Steroids

Number of subjects included in analysis	730
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Treatment difference Arm2-Arm1
Point estimate	6.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.5
upper limit	11.9

Secondary: Clinical acute rejection

End point title	Clinical acute rejection

End point description:

The study analysis population for this endpoint consisted of the ITT set. Patients with no events were censored at the date of last follow-up evaluation or date of death for patients who died or date of graft loss for patients with graft loss. Estimated Kaplan-Meier rates at week 52 have been provided for acute rejection.

End point type	Secondary

End point timeframe:

Up to week 52.

End point values	Advagraf + MMF + Steroids	Advagraf + MMF + Steroids + Sirolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	362	368		
Units: Percentage				
number (not applicable)	7.3	8.3		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Kaplan-Meier survival estimates (percentage) for the rate of patients with the event (Arm 2 minus Arm 1).

Comparison groups	Advagraf + MMF + Steroids v Advagraf + MMF + Steroids + Sirolimus
Number of subjects included in analysis	730
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Treatment difference Arm2-Arm1
Point estimate	1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.9
upper limit	4.9

Secondary: Time to clinical acute rejection

End point title	Time to clinical acute rejection

End point description:

In time-to-event analysis, time to event/censoring was calculated relative to date of reperfusion, defined as Day 0. The study analysis population for this endpoint consisted of subjects with clinical acute rejection.

End point type	Secondary

End point timeframe:

Up to week 52.

End point values	Advagraf + MMF + Steroids	Advagraf + MMF + Steroids + Sirolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	30		
Units: Days				
median (full range (min-max))	82 (28 to 250)	86 (28 to 272)		

Statistical analyses

No statistical analyses for this end point

Secondary: Biopsy Confirmed Acute Rejection (BCAR)

End point title	Biopsy Confirmed Acute Rejection (BCAR)

End point description:

The study analysis population for this endpoint consisted of the ITT set. Patients with no events were censored at the date of last follow-up evaluation or date of death for patients who died or date of graft loss for patients with graft loss. A renal biopsy was performed if clinical and/or laboratory signs indicated the occurrence of a rejection episode. The histological evaluation of the biopsy was performed by the local histopathologist following the 07 Banff criteria classification of renal allograft pathology. Acute rejection which was diagnosed as acute antibody-mediated rejection or acute T-cell-mediated rejection (grades I, II or III) according to the 07 Banff criteria was considered to be BCAR. Estimated Kaplan-Meier rates at week 52 have been provided for BCAR. Overall frequency percentage rates have been provided for Antibody-mediated rejections and T-cell-mediated rejection categories.

End point type	Secondary

End point timeframe:

Up to week 52.

End point values	Advagraf + MMF + Steroids	Advagraf + MMF + Steroids + Sirolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	362	368		
Units: Percentage				
number (not applicable)				
BCAR	4.3	3.6		
T-cell mediated BCAR	3.6	3.3		
Antibody mediated BCAR	0.3	0.3		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
Kaplan-Meier survival estimates (percentage) for the rate of patients with the event (Arm 2 minus Arm 1).	
Comparison groups	Advagraf + MMF + Steroids v Advagraf + MMF + Steroids + Sirolimus
Number of subjects included in analysis	730
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Treatment difference Arm2-Arm1
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.6
upper limit	2.3

Secondary: Time to BCAR

End point title	Time to BCAR
End point description:	
In time-to-event analysis, time to event/censoring will be calculated relative to date of reperfusion, defined as Day 0. The study analysis population for this endpoint consisted of subjects with biopsy confirmed acute rejection.	
End point type	Secondary
End point timeframe:	
Up to week 52	

End point values	Advagraf + MMF + Steroids	Advagraf + MMF + Steroids + Sirolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	13		
Units: Days				
median (full range (min-max))	90 (31 to 370)	89 (37 to 272)		

Statistical analyses

No statistical analyses for this end point

Secondary: Categories of clinical acute rejections

End point title	Categories of clinical acute rejections

End point description:

ITT population. Corticosteroid sensitive acute rejection (CSAR): episode treated with new/increased corticosteroids only and has resolved irrespective of any Advagraf/MMF dose changes. Spontaneously resolving acute rejection (SRAR): episode which has not been treated with new/increased corticosteroids, antibodies or any other medication and has resolved irrespective of Advagraf/MMF dose changes. Corticosteroid resistant acute rejection (CRAR): episode which did not resolve following treatment with corticosteroids. Antibody responsive acute rejection (ARAR) episode treated successfully with antibody but no prior steroid administration. Acute rejection episode ongoing unresolved (UAR): episode ongoing/unresolved at graft loss or patient death irrespective of treatment. Other acute rejection (OAR): episode could not be allocated to 1 of the above categories.

End point type	Secondary

End point timeframe:

Up to week 52.

End point values	Advagraf + MMF + Steroids	Advagraf + MMF + Steroids + Sirolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	362	368		
Units: Percentage of participants				
number (not applicable)				
CSAR	3.6	5.7		
SRAR	2.5	1.4		
CRAR	1.1	1.1		
ARAR	0	0		
UAR	0	0		
OAR	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Delayed graft function (DGF)

End point title	Delayed graft function (DGF)

End point description:

Delayed graft function is defined as the subject having dialysis for more than one day during the first week post kidney transplantation (Day 1 to Day 7). Kaplan-Meier estimates of delayed graft function. Safety analysis set (SAF) population, the SAF population consisted of all patients who took at least 1 dose of any of the study drugs. The values for Kaplan-Meier estimates of delayed graft function are provided post-randomization.

End point type	Secondary

End point timeframe:

Up to week 52.

End point values	Advagraf + MMF + Steroids	Advagraf + MMF + Steroids + Sirolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	362	368		
Units: Percententage rate				
number (confidence interval 95%)	11.9 (9 to 15.7)	11.1 (8.3 to 14.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Subject survival

End point title	Subject survival

End point description:

Patient survival, defined as the time from the day of the first dose of study drug to the day of death (inclusive). Subjects who were alive at the end of the study or at the date of last evaluation were censored. The study analysis population for this endpoint consisted of the ITT set. Patients with no events were censored at the date of last follow-up evaluation or date of death for patients who died or date of graft loss for patients with graft loss. Estimated Kaplan-Meier rates at week 52 have been provided for subject survival.

End point type	Secondary

End point timeframe:

Up to week 52.

End point values	Advagraf + MMF + Steroids	Advagraf + MMF + Steroids + Sirolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	362	368		
Units: Percentage				
number (confidence interval 95%)	98.9 (97 to 99.6)	99.7 (98.1 to 100)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
Kaplan-Meier survival estimates (percentage) for the rate of patients with the event (Arm 2 minus Arm 1).	
Comparison groups	Advagraf + MMF + Steroids v Advagraf + MMF + Steroids + Sirolimus
Number of subjects included in analysis	730
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Treatment difference Arm2-Arm1
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	2.1

Secondary: Graft survival	
End point title	Graft survival
End point description:	
Graft survival, defined as time from the day of reperfusion to the day of graft loss for patients who were transplanted. The study analysis population for this endpoint consisted of the ITT set. Patients with no events were censored at the date of last follow-up evaluation or date of death for patients who died or date of graft loss for patients with graft loss. Estimated Kaplan-Meier rates at week 52 have been provided for graft survival.	
End point type	Secondary
End point timeframe:	
Up to week 52.	

End point values	Advagraf + MMF + Steroids	Advagraf + MMF + Steroids + Sirolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	362	368		
Units: Percentage				
number (confidence interval 95%)	97.1 (94.7 to 98.4)	97.8 (95.6 to 98.9)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
Kaplan-Meier survival estimates (percentage) for the rate of patients with the event (Arm 2 minus Arm 1).	
Comparison groups	Advagraf + MMF + Steroids v Advagraf + MMF + Steroids + Sirolimus
Number of subjects included in analysis	730
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Treatment difference Arm2-Arm1
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	3

Secondary: New Onset Diabetes Mellitus (NODM)

End point title	New Onset Diabetes Mellitus (NODM)
End point description:	
NODM as per American Diabetic Association (ADA) criteria. The study analysis population for this endpoint consisted of the ITT set. Patients with no events were censored at the date of last follow-up evaluation or date of death for patients who died or date of graft loss for patients with graft loss. Estimated Kaplan-Meier rates at week 52 have been provided for NODM.	
End point type	Secondary
End point timeframe:	
Up to week 52.	

End point values	Advagraf + MMF + Steroids	Advagraf + MMF + Steroids + Sirolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	362	368		
Units: Percentage				
number (not applicable)	8.5	12.8		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
Kaplan-Meier survival estimates (percentage) for the rate of patients with the event (Arm 2 minus Arm 1).	
Comparison groups	Advagraf + MMF + Steroids v Advagraf + MMF + Steroids + Sirolimus
Number of subjects included in analysis	730
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Treatment difference Arm2-Arm1
Point estimate	4.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	9.5

Secondary: Safety as assessed by recording adverse events, laboratory assessments and vital signs

End point title	Safety as assessed by recording adverse events, laboratory assessments and vital signs
End point description:	
Treatment-emergent adverse events (TEAEs) were defined as those with an onset date occurring on or after randomization (day 28). AEs which changed in severity on/after the date of randomization were included as TEAEs. ITT population.	
End point type	Secondary
End point timeframe:	
Up to week 52.	

End point values	Advagraf + MMF + Steroids	Advagraf + MMF + Steroids + Sirolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	362	368		
Units: Participants				
TEAEs	307	309		
Drug-related TEAEs	212	215		
Deaths	2	1		
Serious TEAEs	158	148		
Drug-related serious TEAEs	82	77		
TEAEs leading to permanent disc. of drug	22	48		
Drug-related TEAEs leading to perm. disc. or drug	16	39		
Serious TEAEs leading to perm. disc. of drug	11	21		

Drug-related serious TEAEs leading to perm. disc.	7	16		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

TEAEs were defined as those with an onset date occurring on or after randomization (day 28). AEs which changed in severity on/after the date of randomization were included as TEAEs.

Adverse event reporting additional description:

An AE was defined as any untoward medical occurrence in a patient administered a study drug and which did not necessarily have a causal relationship with this treatment. ITT population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Advagraf + MMF + Steroids

Reporting group description:

Arm 1 served as the reference arm for the study; the combination of tacrolimus and MMF has a proven efficacy and safety profile.

Reporting group title	Advagraf + MMF + Steroids + Sirolimus

Reporting group description:

Arm 2 Advagraf + MMF(withdrawn on Day 28) + Steroids + Sirolimus(introduced on Day 28) in combination with lower tacrolimus exposure at Day 42 (week 6) was compared to Arm 1.

Serious adverse events	Advagraf + MMF + Steroids	Advagraf + MMF + Steroids + Sirolimus	
Total subjects affected by serious adverse events			
subjects affected / exposed	158 / 362 (43.65%)	148 / 368 (40.22%)	
number of deaths (all causes)	4	1	
number of deaths resulting from adverse events	1	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 362 (0.28%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraductal papilloma of breast			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastasis			

subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Testicular germ cell cancer			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid cancer			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulval cancer			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Arteriovenous fistula			
subjects affected / exposed	1 / 362 (0.28%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 362 (0.00%)	4 / 368 (1.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	2 / 362 (0.55%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			

subjects affected / exposed	0 / 362 (0.00%)	2 / 368 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphocele			
subjects affected / exposed	5 / 362 (1.38%)	8 / 368 (2.17%)	
occurrences causally related to treatment / all	1 / 5	4 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Microangiopathy			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	2 / 362 (0.55%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			

subjects affected / exposed	1 / 362 (0.28%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			
subjects affected / exposed	1 / 362 (0.28%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Catheter removal			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrectomy			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Removal of ambulatory peritoneal catheter			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthermia			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired healing			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Mucosal haemorrhage			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	3 / 362 (0.83%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	1 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulcer			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (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 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney transplant rejection			
subjects affected / exposed	15 / 362 (4.14%)	11 / 368 (2.99%)	
occurrences causally related to treatment / all	7 / 15	5 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transplant rejection			
subjects affected / exposed	2 / 362 (0.55%)	3 / 368 (0.82%)	
occurrences causally related to treatment / all	1 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Menometrorrhagia			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Prostatitis			
subjects affected / exposed	1 / 362 (0.28%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Testicular haemorrhage			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	1 / 362 (0.28%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 362 (0.55%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lung disorder			
subjects affected / exposed	2 / 362 (0.55%)	2 / 368 (0.54%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Organising pneumonia			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuritic pain			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary arterial hypertension			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	3 / 362 (0.83%)	4 / 368 (1.09%)	
occurrences causally related to treatment / all	1 / 3	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			

Anxiety			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Antibody test positive			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriogram			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial culture positive			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatine increased			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	14 / 362 (3.87%)	20 / 368 (5.43%)	
occurrences causally related to treatment / all	7 / 14	12 / 24	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood glucose increased			
subjects affected / exposed	0 / 362 (0.00%)	2 / 368 (0.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood parathyroid hormone increased			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

C-reactive protein increased			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
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 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Histology abnormal			
subjects affected / exposed	2 / 362 (0.55%)	5 / 368 (1.36%)	
occurrences causally related to treatment / all	2 / 2	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immunosuppressant drug level increased			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Arteriovenous fistula thrombosis			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complications of transplanted kidney			
subjects affected / exposed	6 / 362 (1.66%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	1 / 6	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device dislocation			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Drug misuse			
subjects affected / exposed	0 / 362 (0.00%)	3 / 368 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (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	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	0 / 362 (0.00%)	2 / 368 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perinephric collection			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal graft loss			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shunt blood flow excessive			

subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shunt malfunction			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shunt thrombosis			
subjects affected / exposed	1 / 362 (0.28%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stent occlusion			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haemorrhage			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Therapeutic agent toxicity			
subjects affected / exposed	3 / 362 (0.83%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transplant failure			
subjects affected / exposed	3 / 362 (0.83%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	1 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			

subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric anastomosis complication			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound evisceration			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Gastrointestinal angiodysplasia			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Angina pectoris			
subjects affected / exposed	2 / 362 (0.55%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Atrial fibrillation			
subjects affected / exposed	2 / 362 (0.55%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	2 / 362 (0.55%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 362 (0.28%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart valve incompetence			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 362 (0.28%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sick sinus syndrome			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular extrasystoles			

subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Brain stem haemorrhage			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar radiculopathy			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post herpetic neuralgia			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			

subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Agranulocytosis			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	3 / 362 (0.83%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	2 / 362 (0.55%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 362 (0.28%)	2 / 368 (0.54%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocythaemia			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 362 (0.28%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Cataract			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinopathy proliferative			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous haemorrhage			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	1 / 362 (0.28%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 362 (0.28%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal strangulated hernia			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal wall haematoma			

subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphthous stomatitis			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	3 / 362 (0.83%)	3 / 368 (0.82%)	
occurrences causally related to treatment / all	3 / 3	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric antral vascular ectasia			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernial eventration			
subjects affected / exposed	2 / 362 (0.55%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	2 / 362 (0.55%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal haemorrhage			

subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	4 / 362 (1.10%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute prerenal failure			
subjects affected / exposed	0 / 362 (0.00%)	2 / 368 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anuria			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysuria			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glomerulonephritis			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Glomerulonephritis membranoproliferative			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (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	3 / 362 (0.83%)	2 / 368 (0.54%)	
occurrences causally related to treatment / all	0 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	6 / 362 (1.66%)	2 / 368 (0.54%)	
occurrences causally related to treatment / all	0 / 7	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperoxaluria			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney fibrosis			
subjects affected / exposed	1 / 362 (0.28%)	2 / 368 (0.54%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephropathy toxic			
subjects affected / exposed	3 / 362 (0.83%)	2 / 368 (0.54%)	
occurrences causally related to treatment / all	3 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive uropathy			
subjects affected / exposed	2 / 362 (0.55%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proteinuria			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal artery stenosis			

subjects affected / exposed	1 / 362 (0.28%)	2 / 368 (0.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal artery thrombosis			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	2 / 362 (0.55%)	2 / 368 (0.54%)	
occurrences causally related to treatment / all	1 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	9 / 362 (2.49%)	14 / 368 (3.80%)	
occurrences causally related to treatment / all	4 / 9	7 / 19	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	6 / 362 (1.66%)	5 / 368 (1.36%)	
occurrences causally related to treatment / all	3 / 6	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubulointerstitial nephritis			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteral disorder			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteral polyp			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
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	2 / 362 (0.55%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric stenosis			
subjects affected / exposed	5 / 362 (1.38%)	6 / 368 (1.63%)	
occurrences causally related to treatment / all	0 / 6	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral disorder			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral obstruction			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary fistula			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary incontinence			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	2 / 362 (0.55%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	2 / 362 (0.55%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinoma			

subjects affected / exposed	1 / 362 (0.28%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperparathyroidism			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 362 (0.28%)	2 / 368 (0.54%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle haemorrhage			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteitis			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Abdominal abscess			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BK virus infection			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial pyelonephritis			
subjects affected / exposed	2 / 362 (0.55%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	2 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter intestinal infection			
subjects affected / exposed	2 / 362 (0.55%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridial infection			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus gastritis			

subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus gastroenteritis			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			
subjects affected / exposed	19 / 362 (5.25%)	3 / 368 (0.82%)	
occurrences causally related to treatment / all	14 / 19	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ecthyma			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis enterococcal			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			

subjects affected / exposed	2 / 362 (0.55%)	2 / 368 (0.54%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	5 / 362 (1.38%)	5 / 368 (1.36%)	
occurrences causally related to treatment / all	2 / 5	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	9 / 362 (2.49%)	2 / 368 (0.54%)	
occurrences causally related to treatment / all	5 / 10	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis astroviral			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (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 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis norovirus			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis salmonella			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma infection			

subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis E			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster ophthalmic			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Human polyomavirus infection			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected cyst			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected lymphocele			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	2 / 362 (0.55%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			

subjects affected / exposed	1 / 362 (0.28%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotitis			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis bacterial			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (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	5 / 362 (1.38%)	3 / 368 (0.82%)	
occurrences causally related to treatment / all	3 / 6	2 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pneumonia bacterial			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia cytomegaloviral			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia klebsiella			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia streptococcal			

subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyomavirus-associated nephropathy			
subjects affected / exposed	3 / 362 (0.83%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	2 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	7 / 362 (1.93%)	4 / 368 (1.09%)	
occurrences causally related to treatment / all	2 / 7	5 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	4 / 362 (1.10%)	8 / 368 (2.17%)	
occurrences causally related to treatment / all	3 / 7	4 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis chronic			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cyst infection			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salpingo-oophoritis			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (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	1 / 362 (0.28%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			

subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shunt infection			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal bacteraemia			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Typhoid fever			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 362 (0.55%)	3 / 368 (0.82%)	
occurrences causally related to treatment / all	1 / 3	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			
subjects affected / exposed	2 / 362 (0.55%)	2 / 368 (0.54%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection enterococcal			
subjects affected / exposed	2 / 362 (0.55%)	5 / 368 (1.36%)	
occurrences causally related to treatment / all	1 / 2	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection fungal			
subjects affected / exposed	0 / 362 (0.00%)	2 / 368 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection pseudomonal			

subjects affected / exposed	1 / 362 (0.28%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection staphylococcal			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	5 / 362 (1.38%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	2 / 5	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 362 (0.00%)	2 / 368 (0.54%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	3 / 362 (0.83%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	1 / 362 (0.28%)	3 / 368 (0.82%)	
occurrences causally related to treatment / all	0 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			

subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperlipidaemia			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypervolaemia			
subjects affected / exposed	1 / 362 (0.28%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 362 (0.28%)	0 / 368 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Insulin-requiring type 2 diabetes mellitus			
subjects affected / exposed	0 / 362 (0.00%)	1 / 368 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Advagraf + MMF + Steroids	Advagraf + MMF + Steroids + Sirolimus	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	284 / 362 (78.45%)	284 / 368 (77.17%)	
Investigations			
Blood creatinine increased			
subjects affected / exposed	19 / 362 (5.25%)	13 / 368 (3.53%)	
occurrences (all)	19	13	
Vascular disorders			

Hypertension			
subjects affected / exposed	21 / 362 (5.80%)	20 / 368 (5.43%)	
occurrences (all)	21	22	
Nervous system disorders			
Tremor			
subjects affected / exposed	28 / 362 (7.73%)	26 / 368 (7.07%)	
occurrences (all)	30	26	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	17 / 362 (4.70%)	22 / 368 (5.98%)	
occurrences (all)	18	25	
Leukopenia			
subjects affected / exposed	44 / 362 (12.15%)	9 / 368 (2.45%)	
occurrences (all)	49	9	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	42 / 362 (11.60%)	66 / 368 (17.93%)	
occurrences (all)	47	75	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	45 / 362 (12.43%)	34 / 368 (9.24%)	
occurrences (all)	60	40	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	23 / 362 (6.35%)	14 / 368 (3.80%)	
occurrences (all)	25	14	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	6 / 362 (1.66%)	21 / 368 (5.71%)	
occurrences (all)	6	21	
Infections and infestations			
Cytomegalovirus infection			
subjects affected / exposed	26 / 362 (7.18%)	11 / 368 (2.99%)	
occurrences (all)	28	11	
Escherichia urinary tract infection			
subjects affected / exposed	36 / 362 (9.94%)	19 / 368 (5.16%)	
occurrences (all)	51	23	

Nasopharyngitis			
subjects affected / exposed	29 / 362 (8.01%)	29 / 368 (7.88%)	
occurrences (all)	40	33	
Urinary tract infection			
subjects affected / exposed	18 / 362 (4.97%)	19 / 368 (5.16%)	
occurrences (all)	22	20	
Urinary tract infection bacterial			
subjects affected / exposed	31 / 362 (8.56%)	16 / 368 (4.35%)	
occurrences (all)	39	24	
Urinary tract infection enterococcal			
subjects affected / exposed	18 / 362 (4.97%)	23 / 368 (6.25%)	
occurrences (all)	22	25	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	13 / 362 (3.59%)	23 / 368 (6.25%)	
occurrences (all)	13	25	
Dyslipidaemia			
subjects affected / exposed	20 / 362 (5.52%)	22 / 368 (5.98%)	
occurrences (all)	20	22	
Hypercholesterolaemia			
subjects affected / exposed	13 / 362 (3.59%)	22 / 368 (5.98%)	
occurrences (all)	13	24	
Hyperlipidaemia			
subjects affected / exposed	12 / 362 (3.31%)	23 / 368 (6.25%)	
occurrences (all)	12	23	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 December 2010	The protocol amendment was signed prior to the first-patient-in date.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported