# 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Arm 2: Advagraf + MMF (withdrawn at day 28) + steroids + sirolimus (introduced at day 28) in combination with reduced Advagraf dose at day 42 (week 6) to achieve lower tacrolimus target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 |
| Not fulfilling inclusion/exclusion criteria | 1 | - |
| Miscellaneous | 5 | 3 |
| Protocol violation | 1 | 3 |
| Withdrawal of consent | 7 | 4 |
| Adverse event | 19 | 53 |
| Retransplantation/graft loss | 2 | 2 |
| 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:<br>H0: Mean iohexol clearance ARM 1 = Mean iohexol clearance rate ARM 2<br>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 | |
| 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 | |
| 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 | |
| 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 | |
| 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 | |
| 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 | |
| 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 | |
| **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 | |
| 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 | |
| **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 | |

| | | | |
|---|---|---|---|
| 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 | |
| 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 | |
| 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 | |
| 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 | |
| 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 | |
| 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 | |
| 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 | |
| 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 | |
| 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 | |
| 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 | |
| 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 | |

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%) | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 21 / 362 (5.80%) | 20 / 368 (5.43%) | |
| occurrences (all) | 21 | 22 | |
| Investigations | | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 19 / 362 (5.25%) | 13 / 368 (3.53%) | |
| occurrences (all) | 19 | 13 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 23 / 362 (6.35%) | 14 / 368 (3.80%) | |
| occurrences (all) | 25 | 14 | |
| 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 | |
| Nervous system disorders | | | |
| Tremor | | | |
| subjects affected / exposed | 28 / 362 (7.73%) | 26 / 368 (7.07%) | |
| occurrences (all) | 30 | 26 | |
| 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 | |
| Renal and urinary disorders | | | |
| Proteinuria | | | |
| subjects affected / exposed | 6 / 362 (1.66%) | 21 / 368 (5.71%) | |
| occurrences (all) | 6 | 21 | |
| 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 | |
| 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<br>subjects affected / exposed<br>occurrences (all) | 31 / 362 (8.56%)<br>39 | 16 / 368 (4.35%)<br>24 | |
| Urinary tract infection enterococcal<br>subjects affected / exposed<br>occurrences (all) | 18 / 362 (4.97%)<br>22 | 23 / 368 (6.25%)<br>25 | |

## 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