



Clinical trial results:

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

Summary

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

Results information

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

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | FG-506-02-43 |
|-----------------------|--------------|

Additional study identifiers

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

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

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

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------------|
| Actual start date of recruitment | 27 September 2005 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

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

Notes:

| Subjects enrolled per age group | |
|---|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 92 |
| Adolescents (12-17 years) | 108 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The study was performed in 32 centers across 13 countries.

Pre-assignment

Screening details:

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

Period 1

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

Blinding implementation details:

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

Arms

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

Arm description:

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

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

Dosage and administration details:

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

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

Dosage and administration details:

MMF (both treatment arms): The initial dose of 600 mg/m² of MMF was to be given pre-operatively. The first postoperative dose of MMF was administered within 12 hours following reperfusion. The daily dose was 1200 mg/m² given in 2 doses (equals 600 mg/m² twice daily) for the first 2 weeks. Thereafter a daily dose was 600 mg/m² given in 2 doses (equals 300 mg/m² twice daily). The total daily dose could be adjusted if medically indicated.

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

| | |
|--------------------------|-----------------------|
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

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

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

Dosage and administration details:

Corticosteroids were not provided as study medication but were administered as additional immunosuppressive treatment. Corticosteroids – for treatment arm 1:

Methylprednisolone or equivalent:

Day 0*: 300-600 mg/m² i.v. bolus followed by oral (*= pre-, intra-, or post-operatively)

Prednisone or equivalent:

Day 1: 60 mg/m² p.o.

Day 2: 40 mg/m² p.o.

Day 3: 30 mg/m² p.o.

Day 4: 20 mg/m² p.o.

Day 5- 183: none

| | |
|------------------|---|
| Arm title | Arm 2: Tacrolimus + MMF + Corticosteroids |
|------------------|---|

Arm description:

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

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

Dosage and administration details:

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

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

Dosage and administration details:

MMF (both treatment arms): The initial dose of 600 mg/m² of MMF was to be given pre-operatively. The first postoperative dose of MMF was administered within 12 hours following reperfusion. The daily dose was 1200 mg/m² given in 2 doses (equals 600 mg/m² twice daily) for the first 2 weeks. Thereafter a daily dose was 600 mg/m² given in 2 doses (equals 300 mg/m² twice daily). The total daily dose could be adjusted if medically indicated.

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

Dosage and administration details:

Corticosteroids were not provided as study medication but were administered as additional immunosuppressive treatment. Corticosteroids – for treatment arm 2:

Methylprednisolone or equivalent:

Day 0*: 300-600 mg/m² i.v. bolus followed by oral (*= pre, intra-, or post-op)

Prednisone or equivalent:

Day 1: 60 mg/m² p.o.

Day 2-7: 40 mg/m² p.o.

Day 8-14: 30 mg/m² p.o.

Day 15-28: 20 mg/m² p.o.

Day 29-42: 10 mg/m² p.o.

Day 43-183: < 10 mg/m² p.o.

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

Baseline characteristics

Reporting groups

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

Reporting group description:

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

| | |
|-----------------------|---|
| Reporting group title | Arm 2: Tacrolimus + MMF + Corticosteroids |
|-----------------------|---|

Reporting group description:

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

| Reporting group values | Arm 1: Tacrolimus+MMF+MAB(Daclizumab)+Corticosteroids(Day 0-4) | Arm 2: Tacrolimus + MMF + Corticosteroids | Total |
|--|---|---|-------|
| Number of subjects | 100 | 100 | 200 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | | | 0 |
| Preterm newborn infants (gestational age < 37 wks) | | | 0 |
| Newborns (0-27 days) | | | 0 |
| Infants and toddlers (28 days-23 months) | | | 0 |
| Children (2-11 years) | | | 0 |
| Adolescents (12-17 years) | | | 0 |
| Adults (18-64 years) | | | 0 |
| From 65-84 years | | | 0 |
| 85 years and over | | | 0 |
| Age continuous | | | |
| Age values are based on the Full Analysis Set (FAS). The FAS contains all randomized and transplanted patients with results attributed to the treatment group that they were randomized to and who received at least one dose of study medication (tacrolimus, MMF, daclizumab or steroids). | | | |
| Units: years | | | |
| arithmetic mean | 10.8 | 11.3 | |
| standard deviation | ± 4.2 | ± 4.1 | - |
| Gender categorical | | | |
| Gender values are based on the FAS. | | | |
| Units: Subjects | | | |
| Female | 32 | 39 | 71 |
| Male | 66 | 59 | 125 |
| Subjects not included in FAS | 2 | 2 | 4 |
| Height | | | |
| Height values are based on the FAS. | | | |
| Units: cm | | | |
| arithmetic mean | 134.4 | 136.8 | |
| standard deviation | ± 24.9 | ± 23.9 | - |

End points

End points reporting groups

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

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

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

End point description:

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

$\Delta \text{SDS} = \text{SDSEOS} - \text{SDS}_{\text{baseline}}$,

Where

$\text{SDS} = (\text{height}_{\text{measured}} - \text{height}_{\text{standard population}}) / \text{SD}_{\text{standard population}}$.

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

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

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

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

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Statistical analysis 1 |
| Statistical analysis description: The two treatment groups will be compared and tested for differences in mean change in height SDS from baseline. The null and alternative hypotheses are: H0: $\mu_{ST} = \mu_{SF}$ versus Ha: $\mu_{ST} \neq \mu_{SF}$, where μ_{ST} and μ_{SF} represent the mean change in height SDS from baseline to EOS in the steroid treated group (ST) and the steroid free group (SF) respectively. | |
| Comparison groups | Arm 1: Tacrolimus+MMF+MAB(Daclizumab)+Corticosteroids(Day 0-4) |
| Number of subjects included in analysis | 184 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[1] |
| P-value | = 0.005 |
| Method | ANCOVA |
| Parameter estimate | Treatment group diff. in adj. mean ch. |
| Point estimate | 0.14 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.04 |
| upper limit | 0.23 |

Notes:

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

Secondary: Number of participants with acute rejections (AR)

| | |
|---|---|
| End point title | Number of participants with acute rejections (AR) |
| End point description: FAS population. SRAR: not treated with new/increasing corticosteroids, antibodies/other meds and resolved regardless of tacrolimus/MMF dose changes. CSAR: treated with new/increased corticosteroids only and resolved, regardless of tacrolimus/MMF dose changes. A corticosteroid resistant acute rejection (CRAR) was defined as a rejection episode which did not resolve following treatment with corticosteroids. Rejection episodes which were initially treated with antibodies only were also be included in this category. Other acute rejection: could not be classified into the above categories. Chronic rejections were identified from biopsy findings and AE reporting during medical review. | |
| End point type | Secondary |
| End point timeframe: Up to 6 months. | |

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

Up to 6 months.

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

Statistical analyses

No statistical analyses for this end point

Secondary: Overall AR episodes

| | |
|-----------------|---------------------|
| End point title | Overall AR episodes |
|-----------------|---------------------|

End point description:

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

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

End point timeframe:

Up to 6 months.

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

Up to 6 months.

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

Up to 6 months.

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

Statistical analyses

No statistical analyses for this end point

Secondary: Overall BPAR episodes

| | |
|-----------------|-----------------------|
| End point title | Overall BPAR episodes |
|-----------------|-----------------------|

End point description:

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

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

End point timeframe:

Up to 6 months.

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

Statistical analyses

No statistical analyses for this end point

Secondary: Severity of BPARs

| | |
|---|-------------------|
| End point title | Severity of BPARs |
| End point description: | |
| The study analysis population for this endpoint consisted of the FAS. The histological evaluation of biopsies for the grade of acute rejections were based on the Banff 97 working classification of renal allograft pathology. | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 6 months. | |

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

Statistical analyses

No statistical analyses for this end point

Secondary: Patient survival

| | |
|-----------------|------------------|
| End point title | Patient survival |
|-----------------|------------------|

End point description:

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

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

End point timeframe:

Up to 6 months.

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

Statistical analyses

No statistical analyses for this end point

Secondary: Graft survival

| | |
|-----------------|----------------|
| End point title | Graft survival |
|-----------------|----------------|

End point description:

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

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

End point timeframe:

Up to 6 months

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

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with adverse events (AEs)

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

End point description:

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

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

End point timeframe:

Up to 6 months.

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

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in serum lipids

| | |
|-----------------|---------------------------------|
| End point title | Absolute change in serum lipids |
|-----------------|---------------------------------|

End point description:

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

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

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

End point timeframe:

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

| End point values | Arm 1: Tacrolimus+M MF+MAB(Dacliz umab)+Cortico steroids(Day 0- 4) | Arm 2: Tacrolimus + MMF + Corticosteroids | | |
|-----------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 98 | 98 | | |
| Units: Participants | 9 | 11 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of DGF

| | |
|---|-----------------|
| End point title | Duration of DGF |
| End point description: The study analysis population for this endpoint consisted of the FAS. | |
| End point type | Secondary |
| End point timeframe: Up to day 7 (week 1), DGF must be within 7 days of transplant . | |

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

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with renal dysfunction

| | |
|---|---|
| End point title | Number of participants with renal dysfunction |
| End point description: The study analysis population for this endpoint consisted of the FAS. Renal dysfunction is defined as GFR < 40 mL/min/1.73m ² (Schwartz formula) at Visit 8 (Month 6). | |
| End point type | Secondary |
| End point timeframe: Up to 6 months. | |

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

Statistical analyses

No statistical analyses for this end point

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

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with hypertension

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

| | | | | |
|-----------------------------|---|--|--|--|
| End point values | Arm 1: Tacrolimus+M MF+MAB(Dacliz umab)+Cortico steroids(Day 0- 4) | Arm 2: Tacrolimus + MMF + Corticosteroids | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 98 | 98 | | |
| Units: Participants | 21 | 25 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first AR

| | |
|--|------------------|
| End point title | Time to first AR |
| End point description: | |
| The study analysis population for this endpoint consisted of subjects with AR. Time to first acute rejection episode was defined as the number of days from reperfusion to the first clinical, laboratory or histological signs that were considered to be related to the first acute rejection episode. | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 6 months. | |

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

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first CRAR

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

End point timeframe:

Up to 6 months.

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

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first BPAR

| | |
|-----------------|--------------------|
| End point title | Time to first BPAR |
|-----------------|--------------------|

End point description:

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

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

End point timeframe:

Up to 6 months.

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

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first BCAR

| | |
|--|--------------------|
| End point title | Time to first BCAR |
| End point description: The study analysis population for this endpoint consisted of subjects with BCAR. Time to first biopsy-proven corticosteroid-resistant acute rejection episode was defined as the number of days from reperfusion to the first clinical, laboratory or histological signs that were considered to be related to the first BCAR episode. | |
| End point type | Secondary |
| End point timeframe: Up to 6 months. | |

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

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

FAS population.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|-----|
| Dictionary version | 8.0 |
|--------------------|-----|

Reporting groups

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

Reporting group description:

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

| | |
|-----------------------|------------------------------------|
| Reporting group title | Tacrolimus + MMF + Corticosteroids |
|-----------------------|------------------------------------|

Reporting group description:

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

| Serious adverse events | Tacrolimus + MMF + MAB (Daclizumab) + Corticosteroids | Tacrolimus + MMF + Corticosteroids | |
|---|---|------------------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 63 / 98 (64.29%) | 60 / 98 (61.22%) | |
| number of deaths (all causes) | 1 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Lymphoproliferative disorder | | | |
| subjects affected / exposed | 2 / 98 (2.04%) | 0 / 98 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 98 (0.00%) | 1 / 98 (1.02%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertension | | | |

| | | | |
|--|----------------|----------------|--|
| subjects affected / exposed | 0 / 98 (0.00%) | 1 / 98 (1.02%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lymphocele | | | |
| subjects affected / exposed | 1 / 98 (1.02%) | 3 / 98 (3.06%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Medical device removal | | | |
| subjects affected / exposed | 0 / 98 (0.00%) | 1 / 98 (1.02%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nephrostomy | | | |
| subjects affected / exposed | 0 / 98 (0.00%) | 1 / 98 (1.02%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stent placement | | | |
| subjects affected / exposed | 0 / 98 (0.00%) | 1 / 98 (1.02%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 98 (1.02%) | 0 / 98 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Implant site effusion | | | |
| subjects affected / exposed | 0 / 98 (0.00%) | 1 / 98 (1.02%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 98 (1.02%) | 0 / 98 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Immune system disorders | | | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 0 / 98 (0.00%) | 1 / 98 (1.02%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Graft loss | | | |
| subjects affected / exposed | 1 / 98 (1.02%) | 0 / 98 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound complication | | | |
| subjects affected / exposed | 1 / 98 (1.02%) | 0 / 98 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Atelectasis | | | |
| subjects affected / exposed | 0 / 98 (0.00%) | 1 / 98 (1.02%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Laryngeal stenosis | | | |
| subjects affected / exposed | 1 / 98 (1.02%) | 0 / 98 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary oedema | | | |
| subjects affected / exposed | 2 / 98 (2.04%) | 0 / 98 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 98 (0.00%) | 1 / 98 (1.02%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Blood creatinine increased | | | |

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

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

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

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

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

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

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

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

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

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

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

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

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

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 98 (0.00%) | 4 / 98 (4.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 4 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetes mellitus insulin-dependent | | | |
| subjects affected / exposed | 0 / 98 (0.00%) | 1 / 98 (1.02%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fluid intake reduced | | | |
| subjects affected / exposed | 1 / 98 (1.02%) | 0 / 98 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Glucose tolerance impaired | | | |
| subjects affected / exposed | 0 / 98 (0.00%) | 1 / 98 (1.02%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypercholesterolaemia | | | |
| subjects affected / exposed | 0 / 98 (0.00%) | 1 / 98 (1.02%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 1 / 98 (1.02%) | 0 / 98 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypervolaemia | | | |
| subjects affected / exposed | 1 / 98 (1.02%) | 0 / 98 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

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