



Clinical trial results:

Astagraf XL® to Understand the Impact of Immunosuppression on De Novo DSA Development and Chronic Immune Activation in Kidney Transplantation

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2018-003867-79 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 14 June 2019 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 28 June 2020 |
| First version publication date | 28 June 2020 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | IDTX-MA-3004 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02723591 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Astellas Pharma Global Development, Inc. |
| Sponsor organisation address | Medical Affairs, Americas, 1 Astellas Way, Northbrook, IL, United States, 60062 |
| Public contact | Clinical Trial Disclosure, Astellas Pharma Global Development, Inc., astellas.resultsdisclosure@astellas.com |
| Scientific contact | Clinical Trial Disclosure, Astellas Pharma Global Development, Inc., 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 | 14 June 2019 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 14 June 2019 |
| 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 incidence of a 2-part composite endpoint consisting of de novo DSA (dnDSA) formation or a designation of immune activation (IA) on peripheral blood molecular profiling in patients maintained on twice daily (BID) tacrolimus versus those maintained on Astagraf XL in the first year post-transplant.

Protection of trial subjects:

This clinical study was written, conducted and reported in accordance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (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 | 09 September 2016 |
| 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 | United States: 599 |
| Worldwide total number of subjects | 599 |
| EEA total number of subjects | 0 |

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) | 571 |
| From 65 to 84 years | 28 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants of ≥ 16 years and ≤ 70 of age requiring kidney transplant were enrolled. Randomization was stratified by alemtuzumab (yes/no), kidney donor profile index (KDPI) (3 levels: N/A [living donors] versus ≤ 50 versus > 50), and human leukocyte antigens (HLA) Class II mismatch (yes/no).

Period 1

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

Arms

| | |
|------------------------------|--|
| Are arms mutually exclusive? | Yes |
| Arm title | Tacrolimus, Extended Release (Astagraf XL®) Once Daily |

Arm description:

Participants received tacrolimus extended release capsule (Astagraf XL) at a starting dose of 0.15 milligram per kilogram (mg/kg), once daily, orally within 48 hours of transplantation (per the treating physician's discretion) for up to 1 year. Dose adjustments were allowed such that participants receiving tacrolimus maintained a minimal trough concentration of 6 nanogram per milliliter (ng/mL) at all times during the study.

| | |
|--|------------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Tacrolimus, Extended Release |
| Investigational medicinal product code | |
| Other name | Astagraf XL |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received tacrolimus extended release (Astagraf XL) at a starting dose of 0.15 mg/kg, once daily, orally within 48 hours of transplantation (per the treating physician's discretion) for up to 1 year. Dose adjustments were allowed such that participants receiving tacrolimus maintained a minimal trough concentration of 6 ng/mL at all times during the study.

| | |
|------------------|---|
| Arm title | Tacrolimus, Immediate Release Twice Daily (BID) |
|------------------|---|

Arm description:

Participants received tacrolimus immediate release capsule as per the institutionally-derived protocol, BID, orally within 48 hours of transplantation (per the treating physician's discretion) for up to 1 year. Dose adjustments were allowed such that participants receiving tacrolimus maintained a minimal trough concentration of 6 ng/mL at all times during the study.

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

Dosage and administration details:

Participants received tacrolimus immediate release as per the institutionally-derived protocol, BID, orally within 48 hours of transplantation (per the treating physician's discretion) for up to 1 year. Dose adjustments were allowed such that participants receiving tacrolimus maintained a minimal trough concentration of 6 ng/mL at all times during the study.

| Number of subjects in period 1 | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) |
|---|---|---|
| | | |
| Started | 300 | 299 |
| Completed | 204 | 198 |
| Not completed | 96 | 101 |
| Adverse event, serious fatal | 2 | 2 |
| Consent withdrawn by subject | 4 | 8 |
| Randomized but Never Received Study Drug | 12 | 12 |
| Adverse event, non-fatal | 48 | 40 |
| Miscellaneous | 5 | 6 |
| Lost to follow-up | 1 | 7 |
| Lack of efficacy | 4 | 3 |
| Protocol deviation | 20 | 23 |

Baseline characteristics

Reporting groups

| | |
|--|--|
| Reporting group title | Tacrolimus, Extended Release (Astagraf XL®) Once Daily |
| Reporting group description: | |
| Participants received tacrolimus extended release capsule (Astagraf XL) at a starting dose of 0.15 milligram per kilogram (mg/kg), once daily, orally within 48 hours of transplantation (per the treating physician's discretion) for up to 1 year. Dose adjustments were allowed such that participants receiving tacrolimus maintained a minimal trough concentration of 6 nanogram per milliliter (ng/mL) at all times during the study. | |
| Reporting group title | Tacrolimus, Immediate Release Twice Daily (BID) |
| Reporting group description: | |
| Participants received tacrolimus immediate release capsule as per the institutionally-derived protocol, BID, orally within 48 hours of transplantation (per the treating physician's discretion) for up to 1 year. Dose adjustments were allowed such that participants receiving tacrolimus maintained a minimal trough concentration of 6 ng/mL at all times during the study. | |

| Reporting group values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | Total |
|---|--|---|-------|
| Number of subjects | 300 | 299 | 599 |
| Age categorical | | | |
| Units: Subjects | | | |
| Age continuous | | | |
| The randomized set consisted of all participants who were randomized to receive the study drug (Astagraf XL or BID tacrolimus). | | | |
| Units: years | | | |
| arithmetic mean | 49 | 48.5 | |
| standard deviation | ± 11.7 | ± 11.6 | - |
| Gender categorical | | | |
| The randomized set consisted of all participants who were randomized to receive the study drug (Astagraf XL or BID tacrolimus). | | | |
| Units: Subjects | | | |
| M | 189 | 208 | 397 |
| F | 111 | 91 | 202 |
| Ethnicity | | | |
| The randomized set consisted of all participants who were randomized to receive the study drug (Astagraf XL or BID tacrolimus). | | | |
| Units: Subjects | | | |
| NOT HISPANIC OR LATINO | 268 | 265 | 533 |
| HISPANIC OR LATINO | 32 | 34 | 66 |
| Race | | | |
| The randomized set consisted of all participants who were randomized to receive the study drug (Astagraf XL or BID tacrolimus). | | | |
| Units: Subjects | | | |
| WHITE | 212 | 200 | 412 |
| BLACK OR AFRICAN AMERICAN | 58 | 67 | 125 |
| ASIAN | 10 | 14 | 24 |

| | | | |
|--|----|----|----|
| AMERICAN INDIAN OR ALASKA NATIVE | 4 | 1 | 5 |
| NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER | 2 | 1 | 3 |
| OTHER | 14 | 16 | 30 |

End points

End points reporting groups

| | |
|--|--|
| Reporting group title | Tacrolimus, Extended Release (Astagraf XL®) Once Daily |
| Reporting group description: Participants received tacrolimus extended release capsule (Astagraf XL) at a starting dose of 0.15 milligram per kilogram (mg/kg), once daily, orally within 48 hours of transplantation (per the treating physician's discretion) for up to 1 year. Dose adjustments were allowed such that participants receiving tacrolimus maintained a minimal trough concentration of 6 nanogram per milliliter (ng/mL) at all times during the study. | |
| Reporting group title | Tacrolimus, Immediate Release Twice Daily (BID) |
| Reporting group description: Participants received tacrolimus immediate release capsule as per the institutionally-derived protocol, BID, orally within 48 hours of transplantation (per the treating physician's discretion) for up to 1 year. Dose adjustments were allowed such that participants receiving tacrolimus maintained a minimal trough concentration of 6 ng/mL at all times during the study. | |

Primary: Percentage of Participants who were Positive for de novo DSA (dnDSA) or Immune Activation (IA) Occurrence

| | |
|--|---|
| End point title | Percentage of Participants who were Positive for de novo DSA (dnDSA) or Immune Activation (IA) Occurrence |
| End point description: DSA was considered as a categorical (binary) variable with positivity determined at a threshold criteria approaching mean fluorescence intensity (MFI)=1000 at any time during the study. IA was considered either present or absent using the Trugraf™ v2.0 molecular assay. A negative designation (Trugraf TX Normal) was referred to as Immune Quiescence (IQ). Due to operating characteristics of the assay, a positive designation was considered evidence of IA in all participants. The Modified Full Analysis Set (mFAS) consisted of all participants who were randomized and who received at least 1 dose of study drug (Astagraf XL or BID tacrolimus), and whose pretransplant cross-matched antibody samples did not demonstrate preformed DSA for the duration of the study. | |
| End point type | Primary |
| End point timeframe: From date of transplant until 1 year | |

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|-----------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 275 | 279 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| percentage of participants | 35.6 | 34.4 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Statistical analysis 1 |
| Statistical analysis description: | |
| Logistic regression with DSA/IA occurrence by Month 12 as response, with treatment group, planned Campath use, KDPI level (as recorded in IVRS), HLA Class II mismatch, recipient age, recipient gender, recipient race, and pre-transplant calculated panel reactivity antibody (cPRA) as fixed effects, and pooled site as a random effect with standard variance components covariance type. | |
| Comparison groups | Tacrolimus, Extended Release (Astagraf XL®) Once Daily v Tacrolimus, Immediate Release Twice Daily (BID) |
| Number of subjects included in analysis | 554 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5777 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.115 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.76 |
| upper limit | 1.636 |

Secondary: Percentage of Participants who were Positive, Negative or Indeterminate for dnDSA Occurrence

| | |
|---|--|
| End point title | Percentage of Participants who were Positive, Negative or Indeterminate for dnDSA Occurrence |
| End point description: | |
| DSA was considered as a categorical (binary) variable with positivity determined at a threshold criteria approaching MFI=1000 at any time during the study. Indeterminate was defined as MFI signal was >1000 and DSA was suspected, but could not be confirmed due to inadequate donor typing. Participants whose samples for the test were not available were reported as unknown. The mFAS consisted of all participants who were randomized and who received at least 1 dose of study drug (Astagraf XL or BID tacrolimus), and whose pretransplant cross-matched antibody samples did not demonstrate preformed DSA for the duration of the study. | |
| End point type | Secondary |
| End point timeframe: | |
| From date of transplant until 1 year | |

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|-----------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 275 | 279 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Positive | 5.5 | 4.3 | | |
| Negative | 90.5 | 92.8 | | |
| Indeterminate | 4 | 2.5 | | |
| Unknown | 0 | 0.4 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Peak Mean Fluorescence Intensity (MFI) of DSA Positive Participants

| | |
|-----------------|---|
| End point title | Peak Mean Fluorescence Intensity (MFI) of DSA Positive Participants |
|-----------------|---|

End point description:

Peak MFI of DSA positive participants was reported. The mFAS consisted of all participants who were randomized and who received at least 1 dose of study drug (Astagraf XL or BID tacrolimus), and whose pretransplant cross-matched antibody samples did not demonstrate preformed DSA for the duration of the study. Only those mFAS participants who tested positive for dnDSA were included in the analyses.

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

End point timeframe:

From date of transplant until 1 year

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|------------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 15 | 12 | | |
| Units: fluorescence intensity unit | | | | |
| median (full range (min-max)) | | | | |
| fluorescence intensity unit | 6119.21 (1320.0 to 29317.6) | 2727.99 (1066.0 to 19971.5) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of DSA Positive Participants with Weak, Moderate and Strong Antibody Strentgh

| | |
|-----------------|--|
| End point title | Percentage of DSA Positive Participants with Weak, Moderate and Strong Antibody Strentgh |
|-----------------|--|

End point description:

DSA was considered as a categorical (binary) variable with positivity determined at a threshold criteria approaching MFI=1000 at any time during the study. The mFAS consisted of all participants who were randomized and who received at least 1 dose of study drug (Astagraf XL or BID tacrolimus), and whose pretransplant cross-matched antibody samples did not demonstrate preformed DSA for the duration of the study. Only those mFAS participants who tested positive for dnDSA were included in the analyses.

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

End point timeframe:
From date of transplant until 1 year

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|-----------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 15 | 12 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Weak | 0 | 0 | | |
| Moderate | 73.3 | 83.3 | | |
| Strong | 26.7 | 16.7 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Statistical analysis 1 |
| Statistical analysis description: P-values obtained from a 2x3 Exact Test of treatment by strength levels. | |
| Comparison groups | Tacrolimus, Extended Release (Astagraf XL®) Once Daily v Tacrolimus, Immediate Release Twice Daily (BID) |
| Number of subjects included in analysis | 27 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6618 |
| Method | Fisher exact |

Secondary: Percentage of DSA Positive Participants with DSA Persistence

| | |
|--|--|
| End point title | Percentage of DSA Positive Participants with DSA Persistence |
| End point description: DSA was regarded as persistent under the following conditions: (i) DSA was detected and remained above the threshold for positivity (MFI = 1000) for two consecutive or nonconsecutive measurements, or (ii) the new appearance of a DSA at the threshold for positivity when preceded by a DSA of a different specificity that had subsequently become non-detectable. The mFAS consisted of all participants who were randomized and who received at least 1 dose of study drug (Astagraf XL or BID tacrolimus), and whose pretransplant cross-matched antibody samples did not demonstrate preformed DSA for the duration of the study. Only those mFAS participants who tested positive for dnDSA were included in the analyses. | |
| End point type | Secondary |
| End point timeframe: From date of transplant until 1 year | |

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|-----------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 15 | 12 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| percentage of participants | 73.3 | 50 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants who were Positive or Negative for Complement Component 1, Q Subcomponent (C1q)-binding DSA

| | |
|-----------------|---|
| End point title | Percentage of Participants who were Positive or Negative for Complement Component 1, Q Subcomponent (C1q)-binding DSA |
|-----------------|---|

End point description:

Percentage of participants who were positive or negative for C1q-binding DSA were reported. The mFAS consisted of all participants who were randomized and who received at least 1 dose of study drug (Astagraf XL or BID tacrolimus), and whose pretransplant cross-matched antibody samples did not demonstrate preformed DSA for the duration of the study.

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

End point timeframe:

From date of transplant until 1 year

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|-----------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 275 | 279 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Positive | 1.8 | 0.4 | | |
| Negative | 98.2 | 99.6 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants who were Positive or Negative for DSA Immunoglobulin G (IgG3) Isotype

| | |
|-----------------|--|
| End point title | Percentage of Participants who were Positive or Negative for |
|-----------------|--|

End point description:

Percentage of participants who were positive or negative for IgG3 isotype were reported. The mFAS consisted of all participants who were randomized and who received at least 1 dose of study drug (Astagraf XL or BID tacrolimus), and whose pretransplant cross-matched antibody samples did not demonstrate preformed DSA for the duration of the study.

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

End point timeframe:

From date of transplant until 1 year

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|-----------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 275 | 279 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Positive | 0.7 | 1.1 | | |
| Negative | 99.3 | 98.9 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of DSA Positive Participants with Human Leukocyte Antigen, Class II, DQ Locus (HLA-DQ)

| | |
|-----------------|---|
| End point title | Percentage of DSA Positive Participants with Human Leukocyte Antigen, Class II, DQ Locus (HLA-DQ) |
|-----------------|---|

End point description:

Percentage of DSA positive participants with HLA-DQ Class-II were reported. The mFAS consisted of all participants who were randomized and who received at least 1 dose of study drug (Astagraf XL or BID tacrolimus), and whose pretransplant cross-matched antibody samples did not demonstrate preformed DSA for the duration of the study. Only those mFAS participants who tested positive for DSA were included in the analyses.

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

End point timeframe:

From date of transplant until 1 year

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|-----------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 15 | 12 | | |
| Units: percentage of participants | | | | |

| | | | | |
|----------------------------|----|----|--|--|
| number (not applicable) | | | | |
| percentage of participants | 40 | 25 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants who were Positive for IA Occurrence from Day 1 to Day 365 visit

| | |
|-----------------|--|
| End point title | Percentage of Participants who were Positive for IA Occurrence from Day 1 to Day 365 visit |
|-----------------|--|

End point description:

IA was considered either present or absent using the Trugraf™ v2.0 molecular assay. A negative designation (Trugraf TX Normal) was referred to as Immune Quiescence (IQ). Due to operating characteristics of the assay, a positive designation was considered evidence of IA in all participants. The mFAS consisted of all participants who were randomized and who received at least 1 dose of study drug (Astagraf XL or BID tacrolimus), and whose pretransplant cross-matched antibody samples did not demonstrate preformed DSA for the duration of the study.

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

End point timeframe:

From day 1 to day 365 visit

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|-----------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 275 | 279 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| percentage of participants | 31.3 | 31.2 | | |

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

Logistic regression with IA occurrence by Month 12 as response, with treatment group, planned Campath use, KDPI level (as recorded in IVRS), HLA Class II mismatch, recipient age, recipient gender, recipient race, and pre-transplant cPRA as fixed effects, and pooled site as a random effect with standard Variance Components covariance type.

| | |
|-------------------|--|
| Comparison groups | Tacrolimus, Extended Release (Astagraf XL®) Once Daily v Tacrolimus, Immediate Release Twice Daily (BID) |
|-------------------|--|

| | |
|---|----------------------|
| Number of subjects included in analysis | 554 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8518 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.038 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.7 |
| upper limit | 1.539 |

Secondary: Percentage of Participants who were Positive for IA Occurrence from Day 30 to Day 365 visit

| | |
|-----------------|---|
| End point title | Percentage of Participants who were Positive for IA Occurrence from Day 30 to Day 365 visit |
|-----------------|---|

End point description:

IA was considered either present or absent using the Trugraf™ v2.0 molecular assay. A negative designation (Trugraf TX Normal) was referred to as Immune Quiescence (IQ). Due to operating characteristics of the assay, a positive designation was considered evidence of IA in all participants. The mFAS consisted of all participants who were randomized and who received at least 1 dose of study drug (Astagraf XL or BID tacrolimus), and whose pretransplant cross-matched antibody samples did not demonstrate preformed DSA for the duration of the study.

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

End point timeframe:

From day 30 to day 365 visit

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|-----------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 275 | 279 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| percentage of participants | 21.8 | 21.9 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with IA Persistence

| | |
|-----------------|--|
| End point title | Percentage of Participants with IA Persistence |
|-----------------|--|

End point description:

IA was regarded as persistent under the following conditions: (i) IA was detected and remained above

the threshold for positivity for two consecutive or non-consecutive measurements, or (ii) the new appearance of an IA at the threshold for positivity when preceded by an IA of a different specificity that had subsequently become non-detectable. The mFAS consisted of all participants who were randomized and who received at least 1 dose of study drug (Astagraf XL or BID tacrolimus), and whose pretransplant cross-matched antibody samples did not demonstrate preformed DSA for the duration of the study.

| | |
|--------------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| From date of transplant until 1 year | |

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|-----------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 275 | 279 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| percentage of participants | 7.3 | 10 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Presence of Transplant Glomerulopathy (TG) on Biopsy

| | |
|-----------------|--|
| End point title | Percentage of Participants with Presence of Transplant Glomerulopathy (TG) on Biopsy |
|-----------------|--|

End point description:

TG was defined as chronic glomerulopathy (cg) >0 on centrally-interpreted institutional protocol biopsy or biopsy obtained for cause during the first year post-transplant with +2 months visit window. The Biopsy Analysis Dataset (BAS) consisted of all mFAS participants who had at least 1 post-transplant central pathology assessment.

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

End point timeframe:

From date of transplant until month 14

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|-----------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 123 | 136 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| percentage of participants | 6.5 | 6.6 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Statistical analysis 1 |
| Statistical analysis description: P-values obtained from a 2-sided Fisher's Exact Test of treatment arm by response. | |
| Comparison groups | Tacrolimus, Extended Release (Astagraf XL®) Once Daily v Tacrolimus, Immediate Release Twice Daily (BID) |
| Number of subjects included in analysis | 259 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 1 |
| Method | Fisher exact |

Secondary: Percentage of Participants with Presence of Microcirculatory Inflammation (MI) on Biopsy

| | |
|--|--|
| End point title | Percentage of Participants with Presence of Microcirculatory Inflammation (MI) on Biopsy |
| End point description: MI was defined as glomerulitis (g) + peritubular capillaritis (ptc) ≥ 2 on centrally-interpreted institutional protocol biopsy or biopsy obtained for cause during the first year post-transplant, with +2 months visit window. The BAS consisted of all mFAS participants who had at least 1 post-transplant central pathology assessment. | |
| End point type | Secondary |
| End point timeframe: From date of transplant until month 14 | |

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|-----------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 123 | 136 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| percentage of participants | 8.9 | 5.9 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Statistical analysis 1 |
| Statistical analysis description: P-values obtained from a 2-sided Fisher's Exact Test of treatment arm by response. | |
| Comparison groups | Tacrolimus, Extended Release (Astagraf XL®) Once Daily v Tacrolimus, Immediate Release Twice Daily (BID) |
| Number of subjects included in analysis | 259 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.475 |
| Method | Fisher exact |

Secondary: Percentage of Participants with Presence of Interstitial Fibrosis and Tubular Atrophy (IFTA) and Inflammation on Biopsy

| | |
|--|---|
| End point title | Percentage of Participants with Presence of Interstitial Fibrosis and Tubular Atrophy (IFTA) and Inflammation on Biopsy |
| End point description: IFTA and inflammation was defined as IFTA positive and inflammation positive (i >0) on centrally-interpreted institutional protocol biopsy or biopsy obtained for cause during the first year posttransplant, with +2 months visit window. The BAS consisted of all mFAS participants who had at least 1 post-transplant central pathology assessment. | |
| End point type | Secondary |
| End point timeframe: From date of transplant until month 14 | |

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|-----------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 123 | 136 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| percentage of participants | 26 | 16.9 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Statistical analysis 1 |
| Statistical analysis description: P-values obtained from a 2-sided Fisher's Exact Test of treatment arm by response. | |
| Comparison groups | Tacrolimus, Extended Release (Astagraf XL®) Once Daily v Tacrolimus, Immediate Release Twice Daily (BID) |

| | |
|---|---------------|
| Number of subjects included in analysis | 259 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0939 |
| Method | Fisher exact |

Secondary: Percentage of Participants with Estimated Glomerular Filtration Rate (eGFR) Threshold of <30 Millimetre per Minute per 1.73 Meter Square (mL/min/1.73m²)

| | |
|-----------------|---|
| End point title | Percentage of Participants with Estimated Glomerular Filtration Rate (eGFR) Threshold of <30 Millimetre per Minute per 1.73 Meter Square (mL/min/1.73m ²) |
|-----------------|---|

End point description:

The eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) formula. The mFAS consisted of all participants who were randomized and who received at least 1 dose of study drug (Astagraf XL or BID tacrolimus), and whose pretransplant cross-matched antibody samples did not demonstrate preformed DSA for the duration of the study.

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

End point timeframe:

At 1 year post transplant

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|-----------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 275 | 279 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| percentage of participants | 1.5 | 1.8 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with eGFR Threshold of <40 mL/min/1.73m²

| | |
|-----------------|---|
| End point title | Percentage of Participants with eGFR Threshold of <40 mL/min/1.73m ² |
|-----------------|---|

End point description:

The eGFR was calculated using the MDRD formula. The mFAS consisted of all participants who were randomized and who received at least 1 dose of study drug (Astagraf XL or BID tacrolimus), and whose pretransplant cross-matched antibody samples did not demonstrate preformed DSA for the duration of the study.

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

End point timeframe:

At 1 year post transplant

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|-----------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 275 | 279 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| percentage of participants | 9.5 | 5.7 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with eGFR Threshold of <50 mL/min/1.73m²

| | |
|--|---|
| End point title | Percentage of Participants with eGFR Threshold of <50 mL/min/1.73m ² |
| End point description: The eGFR was calculated using the MDRD formula. The mFAS consisted of all participants who were randomized and who received at least 1 dose of study drug (Astagraf XL or BID tacrolimus), and whose pretransplant cross-matched antibody samples did not demonstrate preformed DSA for the duration of the study. | |
| End point type | Secondary |
| End point timeframe: At 1 year post transplant | |

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|-----------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 275 | 279 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| percentage of participants | 25.5 | 19.7 | | |

Statistical analyses

| | |
|--|------------------------|
| Statistical analysis title | Statistical analysis 1 |
| Statistical analysis description: Logistic regression with occurrence of eGFR < 50 by Month 12 as response, with treatment group, | |

planned Campath use, KDPI level (as recorded in IVRS), HLA Class II mismatch, recipient age, recipient gender, recipient race, and pre-transplant cPRA as fixed effects, and pooled site as a random effect with standard Variance Components covariance type.

| | |
|---|--|
| Comparison groups | Tacrolimus, Extended Release (Astagraf XL®) Once Daily v Tacrolimus, Immediate Release Twice Daily (BID) |
| Number of subjects included in analysis | 554 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.116 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.431 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.915 |
| upper limit | 2.24 |

Secondary: Percentage of Participants with a Five-point Decline in eGFR

| | |
|--|--|
| End point title | Percentage of Participants with a Five-point Decline in eGFR |
| End point description: | |
| The eGFR was calculated using the MDRD formula. The mFAS consisted of all participants who were randomized and who received at least 1 dose of study drug (Astagraf XL or BID tacrolimus), and whose pretransplant cross-matched antibody samples did not demonstrate preformed DSA for the duration of the study. | |
| End point type | Secondary |
| End point timeframe: | |
| From 30 days post transplant until 1 year | |

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|-----------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 275 | 279 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| percentage of participants | 13.1 | 11.1 | | |

Statistical analyses

| | |
|---|------------------------|
| Statistical analysis title | Statistical analysis 1 |
| Statistical analysis description: | |
| Logistic regression with occurrence of 5-point eGFR decline by Month 12 as response, with treatment group, planned Campath use, KDPI level (as recorded in IVRS), HLA Class II mismatch, recipient age, recipient gender, recipient race, and pre-transplant cPRA as fixed effects, and pooled site as a random effect with standard Variance Components covariance type. | |

| | |
|---|--|
| Comparison groups | Tacrolimus, Extended Release (Astagraf XL®) Once Daily v Tacrolimus, Immediate Release Twice Daily (BID) |
| Number of subjects included in analysis | 554 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4995 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.212 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.693 |
| upper limit | 2.12 |

Secondary: eGFR at Day 30, Day 90, Day 180, Day 270 and Day 365

| | |
|------------------------|--|
| End point title | eGFR at Day 30, Day 90, Day 180, Day 270 and Day 365 |
| End point description: | The eGFR was calculated using the MDRD formula. The mFAS consisted of all participants who were randomized and who received at least 1 dose of study drug (Astagraf XL or BID tacrolimus), and whose pretransplant cross-matched antibody samples did not demonstrate preformed DSA for the duration of the study. mFAS population with available data at each time point. |
| End point type | Secondary |
| End point timeframe: | Day 30, day 90, day 180, day 270 and day 365 |

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|--------------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 265 | 271 | | |
| Units: mL/min/1.73 m ² | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 30 (n= 265, 271) | 50.86 (± 17.27) | 52.72 (± 19.40) | | |
| Day 90 (n=250, 252) | 55.56 (± 16.00) | 57.10 (± 19.99) | | |
| Day 180 (n= 230, 229) | 56.81 (± 15.84) | 58.33 (± 17.51) | | |
| Day 270 (n=215, 212) | 57.19 (± 16.84) | 59.04 (± 18.19) | | |
| Day 365 (n=204, 193) | 58.25 (± 16.51) | 60.94 (± 17.83) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Graft Loss

| | |
|--|--|
| End point title | Percentage of Participants with Graft Loss |
| End point description: Graft loss was defined as re-transplantation, transplant nephrectomy, or a return to dialysis for at least a six week duration, or participants' death. The mFAS consisted of all participants who were randomized and who received at least 1 dose of study drug (Astagraf XL or BID tacrolimus), and whose pretransplant cross-matched antibody samples did not demonstrate preformed DSA for the duration of the study. | |
| End point type | Secondary |
| End point timeframe: From date of transplant until 1 year | |

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|-----------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 275 | 279 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| percentage of participants | 1.5 | 1.4 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants who Died

| | |
|---|-------------------------------------|
| End point title | Percentage of Participants who Died |
| End point description: Percentage of participants who died were reported. The mFAS consisted of all participants who were randomized and who received at least 1 dose of study drug (Astagraf XL or BID tacrolimus), and whose pretransplant cross-matched antibody samples did not demonstrate preformed DSA for the duration of the study. | |
| End point type | Secondary |
| End point timeframe: From date of transplant until 1 year | |

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|-----------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 275 | 279 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| percentage of participants | 0.7 | 0.7 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Biopsy-Proven Acute Rejection (BPAR)

| | |
|-----------------|--|
| End point title | Percentage of Participants with Biopsy-Proven Acute Rejection (BPAR) |
|-----------------|--|

End point description:

Positivity was determined by local biopsy, central pathology, or reported adverse events. The mFAS consisted of all participants who were randomized and who received at least 1 dose of study drug (Astagraf XL or BID tacrolimus), and whose pretransplant cross-matched antibody samples did not demonstrate preformed DSA for the duration of the study.

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

End point timeframe:

From date of transplant until 1 year

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|-----------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 275 | 279 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| percentage of participants | 7.6 | 8.2 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants who were Lost to Follow-up

| | |
|-----------------|---|
| End point title | Percentage of Participants who were Lost to Follow-up |
|-----------------|---|

End point description:

Percentage of participants who were lost to follow-up were reported. The mFAS consisted of all participants who were randomized and who received at least 1 dose of study drug (Astagraf XL or BID tacrolimus), and whose pretransplant cross-matched antibody samples did not demonstrate preformed

DSA for the duration of the study.

| | |
|--------------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| From date of transplant until 1 year | |

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|-----------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 275 | 279 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| percentage of participants | 0 | 0.7 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Either Graft Loss, Death, BPAR or Lost to Follow-up

| | |
|-----------------|---|
| End point title | Percentage of Participants with Either Graft Loss, Death, BPAR or Lost to Follow-up |
|-----------------|---|

End point description:

Percentage of participants with either graft loss, death, BPAR or lost to follow-up were reported. The mFAS consisted of all participants who were randomized and who received at least 1 dose of study drug (Astagraf XL or BID tacrolimus), and whose pretransplant cross-matched antibody samples did not demonstrate preformed DSA for the duration of the study.

| | |
|--------------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| From date of transplant until 1 year | |

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|-----------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 275 | 279 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| percentage of participants | 9.1 | 10.4 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with any Antibody-Mediated Rejection (ABMR)

| | |
|-----------------|--|
| End point title | Percentage of Participants with any Antibody-Mediated Rejection (ABMR) |
|-----------------|--|

End point description:

Percentage of participants with ABMR were reported. Central pathology reading was performed as per the 2007 Update to the Banff '97 classification. A positive assessment is defined as antibody mediated changes that are diagnosed as either acute ABMR or chronic active ABMR. The mFAS consisted of all participants who were randomized and who received at least 1 dose of study drug (Astagraf XL or BID tacrolimus), and whose pretransplant cross-matched antibody samples did not demonstrate preformed DSA for the duration of the study.

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

End point timeframe:

From date of transplant until month 14

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|-----------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 275 | 279 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| percentage of participants | 1.6 | 0.7 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Normal Biopsy Findings

| | |
|-----------------|--|
| End point title | Percentage of Participants with Normal Biopsy Findings |
|-----------------|--|

End point description:

Percentage of participants with normal biopsy findings were reported. The BAS consisted of all mFAS participants who had at least 1 post-transplant central pathology assessment.

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

End point timeframe:

From date of transplant until month 14

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|-----------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 123 | 136 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| percentage of participants | 6.5 | 4.4 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with C4d Deposition without Active Rejection

| | |
|--|---|
| End point title | Percentage of Participants with C4d Deposition without Active Rejection |
| End point description: Percentage of participants with C4d deposition without active rejection were reported. The BAS consisted of all mFAS participants who had at least 1 post-transplant central pathology assessment. | |
| End point type | Secondary |
| End point timeframe: From date of transplant until month 14 | |

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|-----------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 123 | 136 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| percentage of participants | 0.8 | 0.7 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Acute ABMR

| | |
|---|--|
| End point title | Percentage of Participants with Acute ABMR |
| End point description: Percentage of participants with acute ABMR were reported. The BAS consisted of all mFAS participants who had at least 1 post-transplant central pathology assessment. | |
| End point type | Secondary |

End point timeframe:

From date of transplant until month 14

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|-----------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 123 | 136 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| percentage of participants | 1.6 | 0.7 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Grade I, II and III Acute ABMR

| | |
|-----------------|--|
| End point title | Percentage of Participants with Grade I, II and III Acute ABMR |
|-----------------|--|

End point description:

Percentage of participants with grade I, II and III acute ABMR were reported. Central pathology reading was performed as per the 2007 Update to the Banff '97 classification. Acute ABMR was graded as Grade I: acute tubular necrosis-like -like minimal inflammation, Grade II: Capillary and or glomerular inflammation (ptc/g >0) and/or thromboses, and Grade III: arterial - v3. The BAS consisted of all mFAS participants who had at least 1 post-transplant central pathology assessment. Only those BAS participants who had acute AMBR were included in the analyses.

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

End point timeframe:

From date of transplant until month 14

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|-----------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 2 | 1 | | |
| Units: percentage of participants | | | | |
| Grade I | 50 | 0 | | |
| Grade II | 50 | 100 | | |
| Grade III | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Chronic ABMR

| | |
|---|--|
| End point title | Percentage of Participants with Chronic ABMR |
| End point description: Percentage of participants with chronic ABMR were reported. The BAS consisted of all mFAS participants who had at least 1 post-transplant central pathology assessment. | |
| End point type | Secondary |
| End point timeframe: From date of transplant until month 14 | |

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|-----------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 123 | 136 | | |
| Units: percentage of participants | | | | |
| percentage of participants | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Borderline Changes

| | |
|---|--|
| End point title | Percentage of Participants with Borderline Changes |
| End point description: Percentage of participants with borderline changes were reported. The BAS consisted of all mFAS participants who had at least 1 post-transplant central pathology assessment. | |
| End point type | Secondary |
| End point timeframe: From date of transplant until month 14 | |

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|-----------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 123 | 136 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| percentage of participants | 14.6 | 14.7 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Acute T-cell Mediated Rejection (TCMR)

| | |
|-----------------|--|
| End point title | Percentage of Participants with Acute T-cell Mediated Rejection (TCMR) |
|-----------------|--|

End point description:

Percentage of participants with acute TCMR were reported. The BAS consisted of all mFAS participants who had at least 1 post-transplant central pathology assessment.

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

End point timeframe:

From date of transplant until month 14

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|-----------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 123 | 136 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| percentage of participants | 6.5 | 5.9 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Chronic TCMR

| | |
|-----------------|--|
| End point title | Percentage of Participants with Chronic TCMR |
|-----------------|--|

End point description:

Percentage of participants with chronic TCMR were reported. The BAS consisted of all mFAS participants who had at least 1 post-transplant central pathology assessment. Only those BAS participants who had TCMR were included in the analyses.

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

End point timeframe:

From date of transplant until month 14

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|-----------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 | 8 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| percentage of participants | 25 | 12.5 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Grade I, II and III IFTA

| | |
|-----------------|--|
| End point title | Percentage of Participants with Grade I, II and III IFTA |
|-----------------|--|

End point description:

Percentage of participants with Grade I, II and III IFTA were reported. Central pathology reading was performed as per the 2007 Update to the Banff '97 classification. IFTA was graded as Grade I: mild interstitial fibrosis and tubular atrophy (<25% of cortical area), Grade II: moderate interstitial fibrosis and tubular atrophy (26–50% of cortical area), and Grade III: severe interstitial fibrosis and tubular atrophy/ loss (>50% of cortical area). The BAS consisted of all mFAS participants who had at least 1 post-transplant central pathology assessment.

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

End point timeframe:

From date of transplant until month 14

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|-----------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 123 | 136 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Grade I | 54.5 | 56.6 | | |
| Grade II | 18.7 | 15.4 | | |
| Grade III | 5.7 | 6.6 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Any Additional Findings

| | |
|--|---|
| End point title | Percentage of Participants with Any Additional Findings |
| End point description: Percentage of participants with any additional findings (other than normal biopsy, borderline changes, acute and chronic ABMR, Grade I, II, and III ABMR, C4D deposition, acute and chronic TCMR, Grade I, II, and III TCMR, Grade I, II and III IFTA, acute tubular necrosis, interstitial nephritis, pyelonephritis, bk virus, calcineurin inhibitor toxicity, hemolytic uremic syndrome and recurrent disease) were reported. The BAS consisted of all mFAS participants who had at least 1 post-transplant central pathology assessment. | |
| End point type | Secondary |
| End point timeframe: From date of transplant until month 14 | |

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|-----------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 123 | 136 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| percentage of participants | 29.3 | 34.6 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Glomerulitis (g) Biopsy Score Assessed Using Banff Lesion Scores

| | |
|--|--|
| End point title | Percentage of Participants with Glomerulitis (g) Biopsy Score Assessed Using Banff Lesion Scores |
| End point description: Central pathology reading was performed as per the 2007 Update to the Banff '97 classification. Banff Lesion Scores assess the presence and the degree of histopathological changes in the different compartments of renal transplant biopsies, focusing primarily but not exclusively on the diagnostic features seen in rejection. [Roufosse C et. al 2018]. Here, Score 0= No glomerulitis, Score 1= <25% glomerulitis, Score 2= 25 to 75% glomerulitis and Score 3= >75% glomerulitis. The BAS consisted of all mFAS participants who had at least 1 post-transplant central pathology assessment. | |
| End point type | Secondary |
| End point timeframe: From date of transplant until month 14 | |

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|-----------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 123 | 136 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Banff Lesion Score 0 | 89.4 | 90.4 | | |
| Banff Lesion Score 1 | 5.7 | 6.6 | | |
| Banff Lesion Score 2 | 4.1 | 1.5 | | |
| Banff Lesion Score 3 | 0 | 0 | | |
| Not able to score | 0.8 | 1.5 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Statistical analysis 1 |
| Statistical analysis description: | |
| P-values obtained from the Exact Test of treatment arm by Banff scoring levels. | |
| Comparison groups | Tacrolimus, Extended Release (Astagraf XL®) Once Daily v Tacrolimus, Immediate Release Twice Daily (BID) |
| Number of subjects included in analysis | 259 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6327 |
| Method | Fisher exact |

Secondary: Percentage of Participants with Tubulitis (t) Biopsy Score Assessed Using Banff Lesion Scores

| | |
|--|---|
| End point title | Percentage of Participants with Tubulitis (t) Biopsy Score Assessed Using Banff Lesion Scores |
| End point description: | |
| Central pathology reading was performed as per the 2007 Update to the Banff '97 classification. Banff Lesion Scores assess the presence and the degree of histopathological changes in the different compartments of renal transplant biopsies, focusing primarily but not exclusively on the diagnostic features seen in rejection. [Roufosse C et. al 2018]. Here, Score 0= No mononuclear cells in tubules or single focus of tubulitis only, Score 1= Foci with 1 to 4 mononuclear cells/tubular cross section (or 10 tubular cells), Score 2= Foci with 5 to 10 mononuclear cells/tubular cross section (or 10 tubular cells) and Score 3= Foci with >10 mononuclear cells/tubular cross section or the presence of ≥2 areas of tubular basement membrane destruction accompanied by i2/i3 inflammation and t2 elsewhere. The BAS consisted of all mFAS participants who had at least 1 post-transplant central pathology assessment. | |
| End point type | Secondary |
| End point timeframe: | |
| From date of transplant until month 14 | |

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|-----------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 123 | 136 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Banff Lesion Score 0 | 79.7 | 79.4 | | |
| Banff Lesion Score 1 | 16.3 | 15.4 | | |
| Banff Lesion Score 2 | 1.6 | 1.5 | | |
| Banff Lesion Score 3 | 1.6 | 2.9 | | |
| Not able to score | 0.8 | 0.7 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Statistical analysis 1 |
| Statistical analysis description: | |
| P-values obtained from the Exact Test of treatment arm by Banff scoring levels. | |
| Comparison groups | Tacrolimus, Extended Release (Astagraf XL®) Once Daily v Tacrolimus, Immediate Release Twice Daily (BID) |
| Number of subjects included in analysis | 259 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9701 |
| Method | Fisher exact |

Secondary: Percentage of Participants with Intimal Arteritis (v) Biopsy Score Assessed Using Banff Lesion Scores

| | |
|--|---|
| End point title | Percentage of Participants with Intimal Arteritis (v) Biopsy Score Assessed Using Banff Lesion Scores |
| End point description: | |
| Central pathology reading was performed as per the 2007 Update to the Banff '97 classification. Banff Lesion Scores assess the presence and the degree of histopathological changes in the different compartments of renal transplant biopsies, focusing primarily but not exclusively on the diagnostic features seen in rejection. [Roufosse C et. al 2018]. Here, Score 0= No arteritis, Score 1= Mild to moderate intimal arteritis in at least 1 arterial cross section, Score 2= Severe intimal arteritis with at least 25% luminal area lost in at least 1 arterial cross section and Score 3= Transmural arteritis and/or arterial fibrinoid change and medial smooth muscle necrosis with lymphocytic infiltrate in vessel. The BAS consisted of all mFAS participants who had at least 1 post-transplant central pathology assessment. | |
| End point type | Secondary |
| End point timeframe: | |
| From date of transplant until month 14 | |

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|-----------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 123 | 136 | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | | | | |
| Banff Lesion Score 0 | 93.5 | 94.9 | | |
| Banff Lesion Score 1 | 2.4 | 2.2 | | |
| Banff Lesion Score 2 | 2.4 | 0 | | |
| Banff Lesion Score 3 | 0 | 0 | | |
| Not able to score | 1.6 | 2.9 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Statistical analysis 1 |
| Statistical analysis description: | |
| P-values obtained from the Exact Test of treatment arm by Banff scoring levels. | |
| Comparison groups | Tacrolimus, Extended Release (Astagraf XL®) Once Daily v Tacrolimus, Immediate Release Twice Daily (BID) |
| Number of subjects included in analysis | 259 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3127 |
| Method | Fisher exact |

Secondary: Percentage of Participants with Mononuclear Cell Interstitial Inflammation (i) Biopsy Score Assessed Using Banff Lesion Scores

| | |
|---|--|
| End point title | Percentage of Participants with Mononuclear Cell Interstitial Inflammation (i) Biopsy Score Assessed Using Banff Lesion Scores |
| End point description: | |
| Central pathology reading was performed as per the 2007 Update to the Banff '97 classification. Banff Lesion Scores assess the presence and the degree of histopathological changes in the different compartments of renal transplant biopsies, focusing primarily but not exclusively on the diagnostic features seen in rejection. [Roufosse C et. al 2018]. Here, Score 0= No inflammation or in less than 10% of unscarred cortical parenchyma, Score 1= Inflammation in 10 to 25% of unscarred cortical parenchyma, Score 2= Inflammation in 26 to 50% of unscarred cortical parenchyma and Score 3= Inflammation in more than 50% of unscarred cortical parenchyma. The BAS consisted of all mFAS participants who had at least 1 post-transplant central pathology assessment. | |
| End point type | Secondary |
| End point timeframe: | |
| From date of transplant until month 14 | |

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|-----------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 123 | 136 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Banff Lesion Score 0 | 68.3 | 76.5 | | |
| Banff Lesion Score 1 | 26.8 | 17.6 | | |
| Banff Lesion Score 2 | 4.1 | 2.2 | | |
| Banff Lesion Score 3 | 0 | 2.9 | | |
| Not able to score | 0.8 | 0.7 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Statistical analysis 1 |
| Statistical analysis description: | |
| P-values obtained from the Exact Test of treatment arm by Banff scoring levels. | |
| Comparison groups | Tacrolimus, Extended Release (Astagraf XL®) Once Daily v Tacrolimus, Immediate Release Twice Daily (BID) |
| Number of subjects included in analysis | 259 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.083 |
| Method | Fisher exact |

Secondary: Percentage of Participants with Glomerular Basement Membrane Double Contours (cg) Biopsy Score Assessed Using Banff Lesion Scores

| | |
|--|---|
| End point title | Percentage of Participants with Glomerular Basement Membrane Double Contours (cg) Biopsy Score Assessed Using Banff Lesion Scores |
| End point description: | |
| Central pathology reading was performed as per the 2007 Update to the Banff '97 classification. Banff Lesion Scores assess the presence and the degree of histopathological changes in different compartments of renal transplant biopsies, focusing primarily but not exclusively on diagnostic features seen in rejection.[Roufosse C et. al 2018]. Here, Score 0= No GBM double contours by light microscopy(LM) or electron microscopy(EM), Score 1= No GBM double contours by LM but GBM double contours(incomplete or circumferential) in at least 3 glomerular capillaries by EM or GBM double contours in 1-25% of capillary loops in the most affected nonsclerotic glomerulus by LM , Score 2= Double contours affecting 26 to 50% of peripheral capillary loops in most affected glomerulus and Score 3= Double contours affecting more than 50% of peripheral capillary loops in most affected glomerulus. The BAS consisted of all mFAS participants who had at least 1 post-transplant central pathology | |
| End point type | Secondary |
| End point timeframe: | |
| From date of transplant until month 14 | |

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|-----------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 123 | 136 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Banff Lesion Score 0 | 93.5 | 93.4 | | |
| Banff Lesion Score 1 | 5.7 | 3.7 | | |
| Banff Lesion Score 2 | 0 | 1.5 | | |
| Banff Lesion Score 3 | 0 | 0 | | |
| Not able to score | 0.8 | 1.5 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Statistical analysis 1 |
| Statistical analysis description: | |
| P-values obtained from the Exact Test of treatment arm by Banff scoring levels. | |
| Comparison groups | Tacrolimus, Extended Release (Astagraf XL®) Once Daily v Tacrolimus, Immediate Release Twice Daily (BID) |
| Number of subjects included in analysis | 259 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6022 |
| Method | Fisher exact |

Secondary: Percentage of Participants with Tubular Atrophy (ct) Biopsy Score Assessed Using Banff Lesion Scores

| | |
|--|--|
| End point title | Percentage of Participants with Tubular Atrophy (ct) Biopsy Score Assessed Using Banff Lesion Scores |
| End point description: | |
| Central pathology reading was performed as per the 2007 Update to the Banff '97 classification. Banff Lesion Scores assess the presence and the degree of histopathological changes in the different compartments of renal transplant biopsies, focusing primarily but not exclusively on the diagnostic features seen in rejection. [Roufosse C et. al 2018]. Here, Score 0= No tubular atrophy, Score 1= Tubular atrophy involving up to 25% of the area of cortical tubules, Score 2= Tubular atrophy involving 26 to 50% of the area of cortical tubules and Score 3= Tubular atrophy involving in >50% of the area of cortical tubules. The BAS consisted of all mFAS participants who had at least 1 post-transplant central pathology assessment. | |
| End point type | Secondary |
| End point timeframe: | |
| From date of transplant until month 14 | |

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|-----------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 123 | 136 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Banff Lesion Score 0 | 20.3 | 21.3 | | |
| Banff Lesion Score 1 | 53.7 | 55.9 | | |
| Banff Lesion Score 2 | 19.5 | 15.4 | | |
| Banff Lesion Score 3 | 5.7 | 6.6 | | |
| Not able to score | 0.8 | 0.7 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Statistical analysis 1 |
| Comparison groups | Tacrolimus, Extended Release (Astagraf XL®) Once Daily v Tacrolimus, Immediate Release Twice Daily (BID) |
| Number of subjects included in analysis | 259 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[1] |
| P-value | = 0.9249 |
| Method | Fisher exact |

Notes:

[1] - P-values obtained from the Exact Test of treatment arm by Banff scoring levels.

Secondary: Percentage of Participants with Interstitial Fibrosis (ci) Biopsy Score Assessed Using Banff Lesion Scores

| | |
|-----------------|--|
| End point title | Percentage of Participants with Interstitial Fibrosis (ci) Biopsy Score Assessed Using Banff Lesion Scores |
|-----------------|--|

End point description:

Central pathology reading was performed as per the 2007 Update to the Banff '97 classification. Banff Lesion Scores assess the presence and the degree of histopathological changes in the different compartments of renal transplant biopsies, focusing primarily but not exclusively on the diagnostic features seen in rejection. [Roufosse C et. al 2018]. Here, Score 0= Interstitial fibrosis in up to 5% of cortical area, Score 1= Interstitial fibrosis in 6 to 25% of cortical area (mild interstitial fibrosis), Score 2= Interstitial fibrosis in 26 to 50% of cortical area (moderate interstitial fibrosis) and Score 3= Interstitial fibrosis in >50% of cortical area (severe interstitial fibrosis). The BAS consisted of all mFAS participants who had at least 1 post-transplant central pathology assessment.

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

End point timeframe:

From date of transplant until month 14

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|-----------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 123 | 136 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Banff Lesion Score 0 | 21.1 | 20.6 | | |
| Banff Lesion Score 1 | 52.8 | 56.6 | | |
| Banff Lesion Score 2 | 19.5 | 15.4 | | |
| Banff Lesion Score 3 | 5.7 | 6.6 | | |
| Not able to score | 0.8 | 0.7 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Statistical analysis 1 |
| Statistical analysis description: | |
| P-values obtained from the Exact Test of treatment arm by Banff scoring levels. | |
| Comparison groups | Tacrolimus, Extended Release (Astagraf XL®) Once Daily v Tacrolimus, Immediate Release Twice Daily (BID) |
| Number of subjects included in analysis | 259 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9136 |
| Method | Fisher exact |

Secondary: Percentage of Participants with Vascular Fibrous Intimal Thickening (cv) Biopsy Score Assessed Using Banff Lesion Scores

| | |
|---|--|
| End point title | Percentage of Participants with Vascular Fibrous Intimal Thickening (cv) Biopsy Score Assessed Using Banff Lesion Scores |
| End point description: | |
| Central pathology reading was performed as per the 2007 Update to the Banff '97 classification. Banff Lesion Scores assess the presence and the degree of histopathological changes in the different compartments of renal transplant biopsies, focusing primarily but not exclusively on the diagnostic features seen in rejection. [Roufosse C et. al 2018]. Here, Score 0= No chronic vascular changes, Score 1= Vascular narrowing of up to 25% luminal area by fibrointimal thickening, Score 2= Vascular narrowing of 26 to 50% luminal area by fibrointimal thickening and Score 3= Vascular narrowing of more than 50% luminal area by fibrointimal thickening. The BAS consisted of all mFAS participants who had at least 1 post-transplant central pathology assessment. | |
| End point type | Secondary |
| End point timeframe: | |
| From date of transplant until month 14 | |

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|-----------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 123 | 136 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Banff Lesion Score 0 | 33.3 | 36 | | |
| Banff Lesion Score 1 | 40.7 | 41.2 | | |
| Banff Lesion Score 2 | 22 | 17.6 | | |
| Banff Lesion Score 3 | 2.4 | 2.2 | | |
| Not able to score | 1.6 | 2.9 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Statistical analysis 1 |
| Statistical analysis description: | |
| P-values obtained from the Exact Test of treatment arm by Banff scoring levels. | |
| Comparison groups | Tacrolimus, Extended Release (Astagraf XL®) Once Daily v Tacrolimus, Immediate Release Twice Daily (BID) |
| Number of subjects included in analysis | 259 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8789 |
| Method | Fisher exact |

Secondary: Percentage of Participants with Arteriolar Hyalinosis (ah) Biopsy Score Assessed Using Banff Lesion Scores

| | |
|---|--|
| End point title | Percentage of Participants with Arteriolar Hyalinosis (ah) Biopsy Score Assessed Using Banff Lesion Scores |
| End point description: | |
| Central pathology reading was performed as per the 2007 Update to the Banff '97 classification. Banff Lesion Scores assess the presence and the degree of histopathological changes in the different compartments of renal transplant biopsies, focusing primarily but not exclusively on the diagnostic features seen in rejection. [Roufosse C et. al 2018]. Here, Score 0= No periodic acid-Schiff (PAS)-positive hyaline arteriolar thickening, Score 1= Mild to moderate PAS-positive hyaline thickening in at least 1 arteriole, Score 2= Moderate to severe PAS-positive hyaline thickening in more than 1 arteriole and Score 3= Severe PAS-positive hyaline thickening in many arterioles. The BAS consisted of all mFAS participants who had at least 1 post-transplant central pathology assessment. | |
| End point type | Secondary |
| End point timeframe: | |
| From date of transplant until month 14 | |

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|-----------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 123 | 136 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Banff Lesion Score 0 | 91.1 | 86.8 | | |
| Banff Lesion Score 1 | 4.1 | 5.9 | | |
| Banff Lesion Score 2 | 4.1 | 3.7 | | |
| Banff Lesion Score 3 | 0 | 2.2 | | |
| Not able to score | 0.8 | 1.5 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Statistical analysis 1 |
| Statistical analysis description: | |
| P-values obtained from the Exact Test of treatment arm by Banff scoring levels. | |
| Comparison groups | Tacrolimus, Extended Release (Astagraf XL®) Once Daily v Tacrolimus, Immediate Release Twice Daily (BID) |
| Number of subjects included in analysis | 259 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5574 |
| Method | Fisher exact |

Secondary: Percentage of Participants with Peritubular Capillaritis (ptc) Biopsy Score Assessed Using Banff Lesion Scores

| | |
|---|--|
| End point title | Percentage of Participants with Peritubular Capillaritis (ptc) Biopsy Score Assessed Using Banff Lesion Scores |
| End point description: | |
| Central pathology reading was performed as per the 2007 Update to the Banff '97 classification. Banff Lesion Scores assess the presence and the degree of histopathological changes in the different compartments of renal transplant biopsies, focusing primarily but not exclusively on the diagnostic features seen in rejection. [Roufosse C et. al 2018]. Here, Score 0= Maximum number of leukocytes <3, Score 1= At least 1 leukocyte cell in ≥10% of cortical PTCs with 3-4 leukocytes in most severely involved PTC, Score 2= At least 1 leukocyte in ≥10% of cortical PTC with 5-10 leukocytes in most severely involved PTC and Score 3= At least 1 leukocyte in ≥10% of cortical PTC with >10 leukocytes in most severely involved PTC. The BAS consisted of all mFAS participants who had at least 1 post-transplant central pathology assessment. | |
| End point type | Secondary |
| End point timeframe: | |
| From date of transplant until month 14 | |

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|-----------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 123 | 136 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Banff Lesion Score 0 | 91.1 | 90.4 | | |
| Banff Lesion Score 1 | 3.3 | 5.1 | | |
| Banff Lesion Score 2 | 4.9 | 2.9 | | |
| Banff Lesion Score 3 | 0 | 0.7 | | |
| Not able to score | 0.8 | 0.7 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Statistical analysis 1 |
| Statistical analysis description: | |
| P-values obtained from the Exact Test of treatment arm by Banff scoring levels. | |
| Comparison groups | Tacrolimus, Extended Release (Astagraf XL®) Once Daily v Tacrolimus, Immediate Release Twice Daily (BID) |
| Number of subjects included in analysis | 259 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.815 |
| Method | Fisher exact |

Secondary: Percentage of Participants with Mesangial Matrix Expansion (mm) Biopsy Score Assessed Using Banff Lesion Scores

| | |
|--|---|
| End point title | Percentage of Participants with Mesangial Matrix Expansion (mm) Biopsy Score Assessed Using Banff Lesion Scores |
| End point description: | |
| Central pathology reading was performed as per the 2007 Update to the Banff '97 classification. Banff Lesion Scores assess the presence and the degree of histopathological changes in the different compartments of renal transplant biopsies, focusing primarily but not exclusively on the diagnostic features seen in rejection. [Roufosse C et. al 2018]. Here, Score 0= No more than mild mesangial matrix increase in any glomerulus, Score 1= At least moderate mesangial matrix increase in up to 25% of nonsclerotic glomeruli, Score 2= At least moderate mesangial matrix increase in 26% to 50% of nonsclerotic glomeruli and Score 3= At least moderate mesangial matrix increase in >50% of nonsclerotic glomeruli. The BAS consisted of all mFAS participants who had at least 1 post-transplant central pathology assessment. | |
| End point type | Secondary |
| End point timeframe: | |
| From date of transplant until month 14 | |

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|-----------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 123 | 136 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Banff Lesion Score 0 | 87.8 | 91.2 | | |
| Banff Lesion Score 1 | 8.9 | 6.6 | | |
| Banff Lesion Score 2 | 2.4 | 0.7 | | |
| Banff Lesion Score 3 | 0 | 0 | | |
| Not able to score | 0.8 | 1.5 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Statistical analysis 1 |
| Statistical analysis description: | |
| P-values obtained from the Exact Test of treatment arm by Banff scoring levels. | |
| Comparison groups | Tacrolimus, Extended Release (Astagraf XL®) Once Daily v Tacrolimus, Immediate Release Twice Daily (BID) |
| Number of subjects included in analysis | 259 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5673 |
| Method | Fisher exact |

Secondary: Time to First Occurrence of DSA

| | |
|---|---------------------------------|
| End point title | Time to First Occurrence of DSA |
| End point description: | |
| DSA was considered as a categorical (binary) variable with positivity determined at a threshold criteria approaching MFI=1000 at any time during the study. The mFAS consisted of all participants who were randomized and who received at least 1 dose of study drug (Astagraf XL or BID tacrolimus), and whose pretransplant cross-matched antibody samples did not demonstrate preformed DSA for the duration of the study. Here, "99999" denotes data not available as analysis of data was not performed because it was not possible to define the exact date of occurrence since the data only recorded the date of sample collection which could not be interpreted as the date of first occurrence. | |
| End point type | Secondary |
| End point timeframe: | |
| From date of transplant until 1 year | |

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|--------------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 275 | 279 | | |
| Units: days | | | | |
| arithmetic mean (standard deviation) | | | | |
| days | 99999 (± 99999) | 99999 (± 99999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Occurrence of HLA-DQ DSA

| | |
|-----------------|--|
| End point title | Time to First Occurrence of HLA-DQ DSA |
|-----------------|--|

End point description:

Time to first occurrence of HLA-DQ DSA was reported. The mFAS consisted of all participants who were randomized and who received at least 1 dose of study drug (Astagraf XL or BID tacrolimus), and whose pretransplant cross-matched antibody samples did not demonstrate preformed DSA for the duration of the study. Here, "99999" denotes data not available as analysis of data was not performed because it was not possible to define the exact date of occurrence since the data only recorded the date of sample collection which could not be interpreted as the date of first occurrence.

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

End point timeframe:

From date of transplant until 1 year

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|--------------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 275 | 279 | | |
| Units: days | | | | |
| arithmetic mean (standard deviation) | | | | |
| days | 99999 (± 99999) | 99999 (± 99999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Occurrence of C1q-binding DSA

| | |
|-----------------|---|
| End point title | Time to First Occurrence of C1q-binding DSA |
|-----------------|---|

End point description:

Time to first occurrence of C1q-binding DSA was reported. The mFAS consisted of all participants who were randomized and who received at least 1 dose of study drug (Astagraf XL or BID tacrolimus), and whose pretransplant cross-matched antibody samples did not demonstrate preformed DSA for the duration of the study. Here, "99999" denotes data not available as analysis of data was not performed because it was not possible to define the exact date of occurrence since the data only recorded the date of sample collection which could not be interpreted as the date of first occurrence.

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

End point timeframe:

From date of transplant until 1 year

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|--------------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 275 | 279 | | |
| Units: days | | | | |
| arithmetic mean (standard deviation) | | | | |
| days | 99999 (± 99999) | 99999 (± 99999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Occurrence of DSA IgG3 Isotype

| | |
|-----------------|--|
| End point title | Time to First Occurrence of DSA IgG3 Isotype |
|-----------------|--|

End point description:

Time to first occurrence of DSA IgG3 isotype was reported. The mFAS consisted of all participants who were randomized and who received at least 1 dose of study drug (Astagraf XL or BID tacrolimus), and whose pretransplant cross-matched antibody samples did not demonstrate preformed DSA for the duration of the study. Here, "99999" denotes data not available as analysis of data was not performed because it was not possible to define the exact date of occurrence since the data only recorded the date of sample collection which could not be interpreted as the date of first occurrence.

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

End point timeframe:

From date of transplant until 1 year

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|--------------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 275 | 279 | | |
| Units: days | | | | |
| arithmetic mean (standard deviation) | | | | |

| | | | | |
|------|-----------------|-----------------|--|--|
| days | 99999 (± 99999) | 99999 (± 99999) | | |
|------|-----------------|-----------------|--|--|

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Occurrence of IA

| | |
|-----------------|--------------------------------|
| End point title | Time to First Occurrence of IA |
|-----------------|--------------------------------|

End point description:

Time to first occurrence of IA was reported. The mFAS consisted of all participants who were randomized and who received at least 1 dose of study drug (Astagraf XL or BID tacrolimus), and whose pretransplant cross-matched antibody samples did not demonstrate preformed DSA for the duration of the study. Here, "99999" denotes data not available as analysis of data was not performed because it was not possible to define the exact date of occurrence since the data only recorded the date of sample collection which could not be interpreted as the date of first occurrence.

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

End point timeframe:

From date of transplant until 1 year

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|--------------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 275 | 279 | | |
| Units: days | | | | |
| arithmetic mean (standard deviation) | | | | |
| days | 99999 (± 99999) | 99999 (± 99999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Occurrence of TG on Biopsy

| | |
|-----------------|--|
| End point title | Time to First Occurrence of TG on Biopsy |
|-----------------|--|

End point description:

Time to first occurrence of TG on biopsy was reported. The mFAS consisted of all participants who were randomized and who received at least 1 dose of study drug (Astagraf XL or BID tacrolimus), and whose pretransplant cross-matched antibody samples did not demonstrate preformed DSA for the duration of the study. Here, "99999" denotes data not available as analysis of data was not performed because it was not possible to define the exact date of occurrence since the data only recorded the date of sample collection which could not be interpreted as the date of first occurrence.

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

End point timeframe:

From date of transplant until 1 year

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|--------------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 275 | 279 | | |
| Units: days | | | | |
| arithmetic mean (standard deviation) | | | | |
| days | 99999 (± 99999) | 99999 (± 99999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Occurrence of Death

| | |
|-----------------|-----------------------------|
| End point title | Time to Occurrence of Death |
|-----------------|-----------------------------|

End point description:

Time to occurrence of death was reported. The mFAS consisted of all participants who were randomized and who received at least 1 dose of study drug (Astagraf XL or BID tacrolimus), and whose pretransplant cross-matched antibody samples did not demonstrate preformed DSA for the duration of the study. Here, "99999" denotes data not available since median and confidence interval was not estimable (that is, not reached) in either treatment group due to low number of events.

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

End point timeframe:

From date of transplant until 1 year

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|----------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 275 | 279 | | |
| Units: days | | | | |
| median (confidence interval 95%) | | | | |
| days | 99999 (99999 to 99999) | 99999 (99999 to 99999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Occurrence of Local BPAR

| | |
|-----------------|--|
| End point title | Time to First Occurrence of Local BPAR |
|-----------------|--|

End point description:

Time to first occurrence of local BPAR was reported. The mFAS consisted of all participants who were randomized and who received at least 1 dose of study drug (Astagraf XL or BID tacrolimus), and whose pretransplant cross-matched antibody samples did not demonstrate preformed DSA for the duration of the study. Here, "99999" denotes data not available as analysis of data was not performed because it was not possible to define the exact date of occurrence since the data only recorded the date of sample collection which could not be interpreted as the date of first occurrence.

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

End point timeframe:

From date of transplant until 1 year

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|--------------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 275 | 279 | | |
| Units: days | | | | |
| arithmetic mean (standard deviation) | | | | |
| days | 99999 (± 99999) | 99999 (± 99999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Occurrence of Acute Forms of ABMR

| | |
|-----------------|---|
| End point title | Time to First Occurrence of Acute Forms of ABMR |
|-----------------|---|

End point description:

Time to first occurrence of acute forms of ABMR was reported. The mFAS consisted of all participants who were randomized and who received at least 1 dose of study drug (Astagraf XL or BID tacrolimus), and whose pretransplant cross-matched antibody samples did not demonstrate preformed DSA for the duration of the study. Here, "99999" denotes data not available as analysis of data was not performed because it was not possible to define the exact date of occurrence since the data only recorded the date of sample collection which could not be interpreted as the date of first occurrence.

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

End point timeframe:

From date of transplant until 1 year

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|--------------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 275 | 275 | | |
| Units: days | | | | |
| arithmetic mean (standard deviation) | | | | |
| days | 99999 (± 99999) | 99999 (± 99999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Occurrence of Chronic Forms of ABMR

| | |
|-----------------|---|
| End point title | Time to First Occurrence of Chronic Forms of ABMR |
|-----------------|---|

End point description:

Time to first occurrence of chronic forms of ABMR was reported. The mFAS consisted of all participants who were randomized and who received at least 1 dose of study drug (Astagraf XL or BID tacrolimus), and whose pretransplant cross-matched antibody samples did not demonstrate preformed DSA for the duration of the study. Here, "99999" denotes data not available as analysis of data was not performed because it was not possible to define the exact date of occurrence since the data only recorded the date of sample collection which could not be interpreted as the date of first occurrence.

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

End point timeframe:

From date of transplant until 1 year

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|--------------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 275 | 279 | | |
| Units: days | | | | |
| arithmetic mean (standard deviation) | | | | |
| days | 99999 (± 99999) | 99999 (± 99999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Occurrence of Acute TCMR

| | |
|-----------------|--|
| End point title | Time to First Occurrence of Acute TCMR |
|-----------------|--|

End point description:

Time to first occurrence of acute TCMR was reported. The mFAS consisted of all participants who were randomized and who received at least 1 dose of study drug (Astagraf XL or BID tacrolimus), and whose pretransplant cross-matched antibody samples did not demonstrate preformed DSA for the duration of the study. Here, "99999" denotes data not available as analysis of data was not performed because it was not possible to define the exact date of occurrence since the data only recorded the date of sample collection which could not be interpreted as the date of first occurrence.

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

End point timeframe:

From date of transplant until 1 year

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|--------------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 275 | 279 | | |
| Units: days | | | | |
| arithmetic mean (standard deviation) | | | | |
| days | 99999 (± 99999) | 99999 (± 99999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Occurrence of Chronic TCMR

| | |
|-----------------|--|
| End point title | Time to First Occurrence of Chronic TCMR |
|-----------------|--|

End point description:

Time to first occurrence of chronic TCMR was reported. The mFAS consisted of all participants who were randomized and who received at least 1 dose of study drug (Astagraf XL or BID tacrolimus), and whose pretransplant cross-matched antibody samples did not demonstrate preformed DSA for the duration of the study. Here, "99999" denotes data not available as analysis of data was not performed because it was not possible to define the exact date of occurrence since the data only recorded the date of sample collection which could not be interpreted as the date of first occurrence.

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

End point timeframe:

From date of transplant until 1 year

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|--------------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 275 | 279 | | |
| Units: days | | | | |
| arithmetic mean (standard deviation) | | | | |

| | | | | |
|------|-----------------|-----------------|--|--|
| days | 99999 (± 99999) | 99999 (± 99999) | | |
|------|-----------------|-----------------|--|--|

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Occurrence of Borderline Changes

| | |
|--|--|
| End point title | Time to First Occurrence of Borderline Changes |
| End point description: | |
| Time to first occurrence of borderline changes was reported. The mFAS consisted of all participants who were randomized and who received at least 1 dose of study drug (Astagraf XL or BID tacrolimus), and whose pretransplant cross-matched antibody samples did not demonstrate preformed DSA for the duration of the study. Here, "99999" denotes data not available as analysis of data was not performed because it was not possible to define the exact date of occurrence since the data only recorded the date of sample collection which could not be interpreted as the date of first occurrence. | |
| End point type | Secondary |
| End point timeframe: | |
| From date of transplant until 1 year | |

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|--------------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 275 | 279 | | |
| Units: days | | | | |
| arithmetic mean (standard deviation) | | | | |
| days | 99999 (± 99999) | 99999 (± 99999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Occurrence of IFTA

| | |
|--|----------------------------------|
| End point title | Time to First Occurrence of IFTA |
| End point description: | |
| Time to first occurrence of IFTA was reported. The mFAS consisted of all participants who were randomized and who received at least 1 dose of study drug (Astagraf XL or BID tacrolimus), and whose pretransplant cross-matched antibody samples did not demonstrate preformed DSA for the duration of the study. Here, "99999" denotes data not available as analysis of data was not performed because it was not possible to define the exact date of occurrence since the data only recorded the date of sample collection which could not be interpreted as the date of first occurrence. | |
| End point type | Secondary |

End point timeframe:
From date of transplant until 1 year

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|--------------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 275 | 279 | | |
| Units: days | | | | |
| arithmetic mean (standard deviation) | | | | |
| days | 99999 (± 99999) | 99999 (± 99999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Treatment-emergent Adverse Event (TEAEs), Related TEAEs, Treatment-emergent Serious Adverse Event (TESAEs), Related TESAEs, TEAEs leading to discontinuation of study treatment and TEAEs leading to death

| | |
|-----------------|--|
| End point title | Percentage of Participants with Treatment-emergent Adverse Event (TEAEs), Related TEAEs, Treatment-emergent Serious Adverse Event (TESAEs), Related TESAEs, TEAEs leading to discontinuation of study treatment and TEAEs leading to death |
|-----------------|--|

End point description:

A TEAE was defined as an Adverse Event (AE) observed on or after the day of starting the administration of the test drug/comparative drug. The Safety Analysis Set (SAF) consisted of all participants who enrolled into the study and took at least 1 dose of study medication and was used for all safety, tolerability, and medication compliance related variables.

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

End point timeframe:

From first dose of study drug up to 7 days after last dose of study drug (up to 2 years)

| End point values | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | Tacrolimus, Immediate Release Twice Daily (BID) | | |
|-----------------------------------|--|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 288 | 287 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| TEAEs | 99.7 | 98.6 | | |
| TEAEs related to study treatment | 77.8 | 70.7 | | |
| TESAEs | 56.6 | 47.4 | | |

| | | | | |
|--|------|------|--|--|
| TESAEs related to study treatment | 27.4 | 23.7 | | |
| TEAEs causing discontinuation of study treatment | 16.3 | 13.9 | | |
| TEAEs leading to death | 0.7 | 0.7 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug up to 7 days after last dose of study drug (up to 2 years)

Adverse event reporting additional description:

The SAF consisted of all participants who enrolled into the study and took at least 1 dose of study medication and was used for all safety, tolerability, and medication compliance related variables.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 20.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---|
| Reporting group title | Tacrolimus, Immediate Release Twice Daily (BID) |
|-----------------------|---|

Reporting group description:

Participants received tacrolimus immediate release capsule as per the institutionally-derived protocol, BID, orally within 48 hours of transplantation (per the treating physician's discretion) for up to 1 year. Dose adjustments were allowed such that participants receiving tacrolimus maintained a minimal trough concentration of 6 ng/mL at all times during the study.

| | |
|-----------------------|--|
| Reporting group title | Tacrolimus, Extended Release (Astagraf XL®) Once Daily |
|-----------------------|--|

Reporting group description:

Participants received tacrolimus extended release capsule (Astagraf XL) at a starting dose of 0.15 milligram per kilogram (mg/kg), once daily, orally within 48 hours of transplantation (per the treating physician's discretion) for up to 1 year. Dose adjustments were allowed such that participants receiving tacrolimus maintained a minimal trough concentration of 6 nanogram per millilitre (ng/mL) at all times during the study.

| Serious adverse events | Tacrolimus, Immediate Release Twice Daily (BID) | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | |
|---|---|---|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 136 / 287 (47.39%) | 163 / 288 (56.60%) | |
| number of deaths (all causes) | 2 | 2 | |
| number of deaths resulting from adverse events | 2 | 2 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholangiocarcinoma | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|--|-----------------|-----------------|--|
| Diffuse large B-cell lymphoma subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric cancer subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malignant ascites subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to liver subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Papillary thyroid cancer subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Parathyroid tumour benign subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post transplant lymphoproliferative disorder subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal cell carcinoma subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |

| | | | |
|---|-----------------|-----------------|--|
| Arteriosclerosis | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Arteriovenous fistula | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Axillary vein thrombosis | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 5 / 287 (1.74%) | 6 / 288 (2.08%) | |
| occurrences causally related to treatment / all | 1 / 5 | 1 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Extremity necrosis | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 2 / 288 (0.69%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Extrinsic iliac vein compression | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematoma | | | |
| subjects affected / exposed | 2 / 287 (0.70%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhage | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertension | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 4 / 287 (1.39%) | 5 / 288 (1.74%) | |
| occurrences causally related to treatment / all | 2 / 4 | 1 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |
| subjects affected / exposed | 4 / 287 (1.39%) | 2 / 288 (0.69%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemia | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lymphocele | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 2 / 288 (0.69%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral ischaemia | | | |
| subjects affected / exposed | 2 / 287 (0.70%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Steal syndrome | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subclavian vein thrombosis | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombophlebitis superficial | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Therapy change | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| 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 | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chest pain | | | |
| subjects affected / exposed | 5 / 287 (1.74%) | 2 / 288 (0.69%) | |
| occurrences causally related to treatment / all | 1 / 5 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Death | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhagic cyst | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|------------------|------------------|--|
| Implant site extravasation | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Incarcerated hernia | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malaise | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral swelling | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 8 / 287 (2.79%) | 9 / 288 (3.13%) | |
| occurrences causally related to treatment / all | 5 / 11 | 1 / 10 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| 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 | 14 / 287 (4.88%) | 12 / 288 (4.17%) | |
| occurrences causally related to treatment / all | 9 / 17 | 5 / 13 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal transplant failure | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transplant rejection | | | |
| subjects affected / exposed | 2 / 287 (0.70%) | 2 / 288 (0.69%) | |
| occurrences causally related to treatment / all | 1 / 2 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Acquired phimosis | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Scrotal oedema | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Testicular swelling | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (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 respiratory failure | | | |
| subjects affected / exposed | 3 / 287 (1.05%) | 2 / 288 (0.69%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 3 / 287 (1.05%) | 5 / 288 (1.74%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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| Nasal necrosis | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| 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 | 2 / 287 (0.70%) | 3 / 288 (1.04%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary infarction | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (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 | 1 / 287 (0.35%) | 2 / 288 (0.69%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 2 / 288 (0.69%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tachypnoea | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Alcohol withdrawal syndrome | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mental status changes | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 2 / 287 (0.70%) | 2 / 288 (0.69%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Product issues | | | |
| Device dislocation | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 8 / 287 (2.79%) | 10 / 288 (3.47%) | |
| occurrences causally related to treatment / all | 4 / 9 | 6 / 12 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood potassium increased | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium test positive | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| 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 | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immunosuppressant drug level increased | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mycobacterium test positive | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| 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 | | | |
| Abdominal wound dehiscence | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Animal bite | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ankle fracture | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| 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 | 2 / 287 (0.70%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Delayed graft function | | | |
| subjects affected / exposed | 4 / 287 (1.39%) | 5 / 288 (1.74%) | |
| occurrences causally related to treatment / all | 1 / 4 | 1 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fall | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 2 / 288 (0.69%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Foot fracture | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Forearm fracture | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Graft complication | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Incision site pain | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| 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 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Joint dislocation | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Laceration | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Overdose | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 3 / 288 (1.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pelvic fracture | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Perirenal haematoma | | | |
| subjects affected / exposed | 3 / 287 (1.05%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural haematuria | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Procedural pain | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychosis postoperative | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seroma | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 287 (0.35%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thermal burn | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thoracic vertebral fracture | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tibia fracture | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transplant dysfunction | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ureteric anastomosis complication | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular pseudoaneurysm | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (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 / 287 (0.35%) | 3 / 288 (1.04%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound haematoma | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 287 (0.00%) | 2 / 288 (0.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Congenital, familial and genetic disorders | | | |
| Congenital cystic kidney disease | | | |
| subjects affected / exposed | 2 / 287 (0.70%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 2 / 287 (0.70%) | 3 / 288 (1.04%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aortic valve stenosis | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 2 / 287 (0.70%) | 3 / 288 (1.04%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bradycardia | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 3 / 288 (1.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |

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|---|-----------------|-----------------|--|
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Coronary artery disease | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 2 / 288 (0.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Left ventricular failure | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pericardial effusion | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulseless electrical activity | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Supraventricular extrasystoles | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tachycardia | | | |
| subjects affected / exposed | 2 / 287 (0.70%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Carotid artery occlusion | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Central nervous system | | | |

| | | | |
|---|-----------------|-----------------|--|
| haemorrhage | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Central nervous system lesion | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (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 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 2 / 288 (0.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Headache | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertensive encephalopathy | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemic stroke | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolic encephalopathy | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myelopathy | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Posterior reversible encephalopathy syndrome | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Presyncope | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Status epilepticus | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 3 / 287 (1.05%) | 2 / 288 (0.69%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 6 / 287 (2.09%) | 2 / 288 (0.69%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 3 / 287 (1.05%) | 2 / 288 (0.69%) | |
| occurrences causally related to treatment / all | 1 / 4 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhagic anaemia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 287 (0.35%) | 2 / 288 (0.69%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukocytosis | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 2 / 288 (0.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Methaemoglobinaemia | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 2 / 287 (0.70%) | 5 / 288 (1.74%) | |
| occurrences causally related to treatment / all | 0 / 2 | 2 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombotic microangiopathy | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Vertigo positional | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (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 distension | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal hernia | | | |

| | | | |
|---|------------------|-----------------|--|
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain | | | |
| subjects affected / exposed | 6 / 287 (2.09%) | 2 / 288 (0.69%) | |
| occurrences causally related to treatment / all | 1 / 10 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain lower | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 1 / 288 (0.35%) | |
| 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 / 287 (0.00%) | 2 / 288 (0.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis | | | |
| subjects affected / exposed | 2 / 287 (0.70%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 2 / 287 (0.70%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetic gastroparesis | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 11 / 287 (3.83%) | 7 / 288 (2.43%) | |
| occurrences causally related to treatment / all | 5 / 11 | 2 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 287 (0.35%) | 2 / 288 (0.69%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal necrosis | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hiatus hernia | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus | | | |
| subjects affected / exposed | 4 / 287 (1.39%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Impaired gastric emptying | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 2 / 288 (0.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intra-abdominal fluid collection | | | |
| subjects affected / exposed | 3 / 287 (1.05%) | 2 / 288 (0.69%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestine perforation | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Melaena | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 5 / 287 (1.74%) | 4 / 288 (1.39%) | |
| occurrences causally related to treatment / all | 4 / 6 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Obstructive pancreatitis | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Odynophagia | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 3 / 288 (1.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis acute | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Retroperitoneal haematoma | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Retroperitoneal haemorrhage | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 7 / 287 (2.44%) | 4 / 288 (1.39%) | |
| occurrences causally related to treatment / all | 6 / 10 | 1 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Biliary tract disorder | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gallbladder necrosis | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatitis acute | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatitis alcoholic | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| 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 | | | |
| Diabetic foot | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rash | | | |

| | | | |
|---|-------------------|------------------|--|
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin necrosis | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin ulcer | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Swelling face | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 31 / 287 (10.80%) | 26 / 288 (9.03%) | |
| occurrences causally related to treatment / all | 18 / 36 | 12 / 33 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Azotaemia | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 2 / 288 (0.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bladder outlet obstruction | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Focal segmental glomerulosclerosis | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 2 / 288 (0.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematuria | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 287 (0.70%) | 2 / 288 (0.69%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhage urinary tract | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hydronephrosis | | | |
| subjects affected / exposed | 5 / 287 (1.74%) | 3 / 288 (1.04%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Perinephric collection | | | |
| subjects affected / exposed | 5 / 287 (1.74%) | 3 / 288 (1.04%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal artery stenosis | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 2 / 288 (0.69%) | |
| 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 | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal pain | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal tubular injury | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal tubular necrosis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 287 (0.35%) | 2 / 288 (0.69%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal vein thrombosis | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tubulointerstitial nephritis | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ureteric obstruction | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 2 / 288 (0.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ureteric stenosis | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinoma | | | |
| subjects affected / exposed | 2 / 287 (0.70%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |
| Hyperparathyroidism | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperparathyroidism tertiary | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 287 (0.00%) | 2 / 288 (0.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cervical spinal stenosis | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Flank pain | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intervertebral disc degeneration | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mobility decreased | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Muscle haemorrhage | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myalgia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteitis | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 2 / 288 (0.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 2 / 288 (0.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vertebral foraminal stenosis | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Abdominal abscess | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abscess neck | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anal abscess | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arteriovenous fistula site infection | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bacteraemia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 4 / 287 (1.39%) | 4 / 288 (1.39%) | |
| occurrences causally related to treatment / all | 1 / 4 | 2 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 4 / 287 (1.39%) | 4 / 288 (1.39%) | |
| occurrences causally related to treatment / all | 3 / 6 | 1 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium difficile infection | | | |
| subjects affected / exposed | 6 / 287 (2.09%) | 2 / 288 (0.69%) | |
| occurrences causally related to treatment / all | 4 / 6 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coccidioidomycosis | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cystitis | | | |
| subjects affected / exposed | 2 / 287 (0.70%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cytomegalovirus colitis | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (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 | 2 / 287 (0.70%) | 3 / 288 (1.04%) | |
| occurrences causally related to treatment / all | 1 / 2 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cytomegalovirus viraemia | | | |
| subjects affected / exposed | 6 / 287 (2.09%) | 4 / 288 (1.39%) | |
| occurrences causally related to treatment / all | 5 / 6 | 3 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetic foot infection | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Disseminated cytomegaloviral infection | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterobacter bacteraemia | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterococcal bacteraemia | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterococcal sepsis | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterovirus infection | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Escherichia bacteraemia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Escherichia infection | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Escherichia urinary tract infection | | | |
| subjects affected / exposed | 2 / 287 (0.70%) | 3 / 288 (1.04%) | |
| occurrences causally related to treatment / all | 1 / 3 | 3 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fungaemia | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fungal oesophagitis | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gangrene | | | |
| subjects affected / exposed | 2 / 287 (0.70%) | 0 / 288 (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 | 3 / 287 (1.05%) | 3 / 288 (1.04%) | |
| occurrences causally related to treatment / all | 1 / 3 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis norovirus | | | |
| subjects affected / exposed | 2 / 287 (0.70%) | 2 / 288 (0.69%) | |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis viral | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 287 (0.35%) | 4 / 288 (1.39%) | |
| occurrences causally related to treatment / all | 0 / 1 | 3 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Incision site abscess | | | |
| subjects affected / exposed | 2 / 287 (0.70%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infected cyst | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infection in an immunocompromised host | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 2 / 288 (0.69%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Klebsiella bacteraemia | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Localised infection | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 2 / 288 (0.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection bacterial | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lymph node tuberculosis | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Necrotising soft tissue infection | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteomyelitis | | | |
| subjects affected / exposed | 2 / 287 (0.70%) | 3 / 288 (1.04%) | |
| occurrences causally related to treatment / all | 0 / 2 | 2 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Paronychia | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Perirectal abscess | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peritonitis | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peritonitis bacterial | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 7 / 287 (2.44%) | 10 / 288 (3.47%) | |
| occurrences causally related to treatment / all | 4 / 8 | 8 / 11 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia klebsiella | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia legionella | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia pseudomonal | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Polyomavirus-associated nephropathy | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pseudomonal bacteraemia | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis | | | |
| subjects affected / exposed | 2 / 287 (0.70%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 2 / 287 (0.70%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rhinovirus infection | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |

| | | | |
|---|------------------|-----------------|--|
| subjects affected / exposed | 10 / 287 (3.48%) | 7 / 288 (2.43%) | |
| occurrences causally related to treatment / all | 6 / 10 | 3 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic shock | | | |
| subjects affected / exposed | 2 / 287 (0.70%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin infection | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal bacteraemia | | | |
| subjects affected / exposed | 3 / 287 (1.05%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal infection | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Streptococcal urinary tract infection | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tooth infection | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper respiratory tract infection | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 2 / 287 (0.70%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 11 / 287 (3.83%) | 16 / 288 (5.56%) | |
| occurrences causally related to treatment / all | 7 / 12 | 9 / 17 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection bacterial | | | |
| subjects affected / exposed | 2 / 287 (0.70%) | 2 / 288 (0.69%) | |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection enterococcal | | | |
| subjects affected / exposed | 2 / 287 (0.70%) | 2 / 288 (0.69%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urosepsis | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Viral infection | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Viral pharyngitis | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vulval abscess | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vulval cellulitis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound infection | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound infection staphylococcal | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 5 / 287 (1.74%) | 3 / 288 (1.04%) | |
| occurrences causally related to treatment / all | 1 / 7 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 2 / 287 (0.70%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 2 / 288 (0.69%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fluid overload | | | |
| subjects affected / exposed | 2 / 287 (0.70%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycaemia | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 2 / 287 (0.70%) | 7 / 288 (2.43%) | |
| occurrences causally related to treatment / all | 2 / 2 | 4 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycaemic hyperosmolar nonketotic syndrome | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 5 / 287 (1.74%) | 15 / 288 (5.21%) | |
| occurrences causally related to treatment / all | 6 / 6 | 7 / 16 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypernatraemia | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 2 / 288 (0.69%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 2 / 288 (0.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypophosphataemia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypovolaemia | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 2 / 288 (0.69%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lactic acidosis | | | |
| subjects affected / exposed | 1 / 287 (0.35%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malnutrition | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolic acidosis | | | |
| subjects affected / exposed | 2 / 287 (0.70%) | 0 / 288 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Type 1 diabetes mellitus | | | |
| subjects affected / exposed | 0 / 287 (0.00%) | 1 / 288 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Tacrolimus, Immediate Release Twice Daily (BID) | Tacrolimus, Extended Release (Astagraf XL®) Once Daily | |
|---|---|---|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 278 / 287 (96.86%) | 285 / 288 (98.96%) | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 50 / 287 (17.42%) | 53 / 288 (18.40%) | |
| occurrences (all) | 53 | 57 | |

| | | | |
|---|-------------------------|-------------------------|--|
| Hypotension subjects affected / exposed occurrences (all) | 45 / 287 (15.68%) 51 | 41 / 288 (14.24%) 44 | |
| Orthostatic hypotension subjects affected / exposed occurrences (all) | 19 / 287 (6.62%) 20 | 13 / 288 (4.51%) 14 | |
| General disorders and administration site conditions | | | |
| Asthenia subjects affected / exposed occurrences (all) | 14 / 287 (4.88%) 15 | 21 / 288 (7.29%) 23 | |
| Chest pain subjects affected / exposed occurrences (all) | 12 / 287 (4.18%) 12 | 15 / 288 (5.21%) 15 | |
| Fatigue subjects affected / exposed occurrences (all) | 45 / 287 (15.68%) 51 | 45 / 288 (15.63%) 48 | |
| Oedema subjects affected / exposed occurrences (all) | 17 / 287 (5.92%) 18 | 10 / 288 (3.47%) 12 | |
| Oedema peripheral subjects affected / exposed occurrences (all) | 53 / 287 (18.47%) 64 | 53 / 288 (18.40%) 63 | |
| Pyrexia subjects affected / exposed occurrences (all) | 38 / 287 (13.24%) 44 | 28 / 288 (9.72%) 37 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough subjects affected / exposed occurrences (all) | 20 / 287 (6.97%) 22 | 26 / 288 (9.03%) 26 | |
| Dyspnoea subjects affected / exposed occurrences (all) | 30 / 287 (10.45%) 38 | 32 / 288 (11.11%) 34 | |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 21 / 287 (7.32%) 22 | 23 / 288 (7.99%) 27 | |
| Psychiatric disorders | | | |

| | | | |
|--|--------------------------|-------------------------|--|
| Anxiety subjects affected / exposed occurrences (all) | 24 / 287 (8.36%) 29 | 12 / 288 (4.17%) 14 | |
| Insomnia subjects affected / exposed occurrences (all) | 44 / 287 (15.33%) 47 | 40 / 288 (13.89%) 42 | |
| Investigations Blood creatinine increased subjects affected / exposed occurrences (all) | 43 / 287 (14.98%) 49 | 37 / 288 (12.85%) 40 | |
| Viral test positive subjects affected / exposed occurrences (all) | 18 / 287 (6.27%) 18 | 10 / 288 (3.47%) 11 | |
| Weight increased subjects affected / exposed occurrences (all) | 14 / 287 (4.88%) 14 | 16 / 288 (5.56%) 18 | |
| Injury, poisoning and procedural complications Delayed graft function subjects affected / exposed occurrences (all) | 30 / 287 (10.45%) 30 | 15 / 288 (5.21%) 15 | |
| Incision site pain subjects affected / exposed occurrences (all) | 47 / 287 (16.38%) 50 | 24 / 288 (8.33%) 25 | |
| Procedural pain subjects affected / exposed occurrences (all) | 91 / 287 (31.71%) 105 | 55 / 288 (19.10%) 62 | |
| Cardiac disorders Tachycardia subjects affected / exposed occurrences (all) | 24 / 287 (8.36%) 25 | 27 / 288 (9.38%) 28 | |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) | 30 / 287 (10.45%) 36 | 34 / 288 (11.81%) 41 | |
| Headache | | | |

| | | | |
|--|---------------------------|---------------------------|--|
| subjects affected / exposed occurrences (all) | 38 / 287 (13.24%) 43 | 46 / 288 (15.97%) 58 | |
| Tremor subjects affected / exposed occurrences (all) | 84 / 287 (29.27%) 89 | 94 / 288 (32.64%) 99 | |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 37 / 287 (12.89%) 45 | 42 / 288 (14.58%) 46 | |
| Leukocytosis subjects affected / exposed occurrences (all) | 21 / 287 (7.32%) 23 | 12 / 288 (4.17%) 12 | |
| Leukopenia subjects affected / exposed occurrences (all) | 58 / 287 (20.21%) 67 | 66 / 288 (22.92%) 74 | |
| Neutropenia subjects affected / exposed occurrences (all) | 28 / 287 (9.76%) 30 | 20 / 288 (6.94%) 23 | |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 18 / 287 (6.27%) 18 | 14 / 288 (4.86%) 14 | |
| Gastrointestinal disorders | | | |
| Abdominal distension subjects affected / exposed occurrences (all) | 21 / 287 (7.32%) 27 | 14 / 288 (4.86%) 15 | |
| Abdominal pain subjects affected / exposed occurrences (all) | 35 / 287 (12.20%) 39 | 31 / 288 (10.76%) 34 | |
| Constipation subjects affected / exposed occurrences (all) | 100 / 287 (34.84%) 113 | 90 / 288 (31.25%) 101 | |
| Diarrhoea subjects affected / exposed occurrences (all) | 115 / 287 (40.07%) 160 | 128 / 288 (44.44%) 165 | |
| Dyspepsia | | | |

| | | | |
|--|---------------------------|---------------------------|--|
| subjects affected / exposed occurrences (all) | 24 / 287 (8.36%) 29 | 24 / 288 (8.33%) 26 | |
| Gastrooesophageal reflux disease subjects affected / exposed occurrences (all) | 9 / 287 (3.14%) 9 | 15 / 288 (5.21%) 18 | |
| Nausea subjects affected / exposed occurrences (all) | 104 / 287 (36.24%) 133 | 101 / 288 (35.07%) 131 | |
| Vomiting subjects affected / exposed occurrences (all) | 61 / 287 (21.25%) 77 | 41 / 288 (14.24%) 54 | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia subjects affected / exposed occurrences (all) | 15 / 287 (5.23%) 15 | 24 / 288 (8.33%) 24 | |
| Pruritus subjects affected / exposed occurrences (all) | 21 / 287 (7.32%) 23 | 18 / 288 (6.25%) 18 | |
| Renal and urinary disorders | | | |
| Dysuria subjects affected / exposed occurrences (all) | 21 / 287 (7.32%) 23 | 27 / 288 (9.38%) 30 | |
| Haematuria subjects affected / exposed occurrences (all) | 30 / 287 (10.45%) 30 | 25 / 288 (8.68%) 26 | |
| Proteinuria subjects affected / exposed occurrences (all) | 15 / 287 (5.23%) 15 | 5 / 288 (1.74%) 5 | |
| Urinary retention subjects affected / exposed occurrences (all) | 18 / 287 (6.27%) 18 | 13 / 288 (4.51%) 14 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 16 / 287 (5.57%) 22 | 14 / 288 (4.86%) 18 | |
| Back pain | | | |

| | | | |
|------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed | 17 / 287 (5.92%) | 19 / 288 (6.60%) | |
| occurrences (all) | 17 | 20 | |
| Muscle spasms | | | |
| subjects affected / exposed | 21 / 287 (7.32%) | 12 / 288 (4.17%) | |
| occurrences (all) | 22 | 12 | |
| Pain in extremity | | | |
| subjects affected / exposed | 23 / 287 (8.01%) | 17 / 288 (5.90%) | |
| occurrences (all) | 27 | 20 | |
| Infections and infestations | | | |
| BK virus infection | | | |
| subjects affected / exposed | 37 / 287 (12.89%) | 45 / 288 (15.63%) | |
| occurrences (all) | 37 | 47 | |
| Cytomegalovirus viraemia | | | |
| subjects affected / exposed | 15 / 287 (5.23%) | 18 / 288 (6.25%) | |
| occurrences (all) | 15 | 21 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 17 / 287 (5.92%) | 21 / 288 (7.29%) | |
| occurrences (all) | 19 | 23 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 31 / 287 (10.80%) | 25 / 288 (8.68%) | |
| occurrences (all) | 32 | 27 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 44 / 287 (15.33%) | 50 / 288 (17.36%) | |
| occurrences (all) | 77 | 65 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 20 / 287 (6.97%) | 12 / 288 (4.17%) | |
| occurrences (all) | 20 | 14 | |
| Dehydration | | | |
| subjects affected / exposed | 21 / 287 (7.32%) | 14 / 288 (4.86%) | |
| occurrences (all) | 23 | 14 | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 19 / 287 (6.62%) | 18 / 288 (6.25%) | |
| occurrences (all) | 19 | 19 | |
| Hypercalcaemia | | | |

| | | |
|-----------------------------|--------------------|--------------------|
| subjects affected / exposed | 18 / 287 (6.27%) | 14 / 288 (4.86%) |
| occurrences (all) | 18 | 15 |
| Hyperglycaemia | | |
| subjects affected / exposed | 58 / 287 (20.21%) | 37 / 288 (12.85%) |
| occurrences (all) | 62 | 41 |
| Hyperkalaemia | | |
| subjects affected / exposed | 79 / 287 (27.53%) | 81 / 288 (28.13%) |
| occurrences (all) | 102 | 106 |
| Hyperphosphataemia | | |
| subjects affected / exposed | 21 / 287 (7.32%) | 18 / 288 (6.25%) |
| occurrences (all) | 22 | 20 |
| Hypocalcaemia | | |
| subjects affected / exposed | 41 / 287 (14.29%) | 37 / 288 (12.85%) |
| occurrences (all) | 42 | 43 |
| Hypoglycaemia | | |
| subjects affected / exposed | 16 / 287 (5.57%) | 12 / 288 (4.17%) |
| occurrences (all) | 20 | 14 |
| Hypokalaemia | | |
| subjects affected / exposed | 37 / 287 (12.89%) | 38 / 288 (13.19%) |
| occurrences (all) | 44 | 39 |
| Hypomagnesaemia | | |
| subjects affected / exposed | 124 / 287 (43.21%) | 124 / 288 (43.06%) |
| occurrences (all) | 143 | 142 |
| Hyponatraemia | | |
| subjects affected / exposed | 18 / 287 (6.27%) | 19 / 288 (6.60%) |
| occurrences (all) | 18 | 21 |
| Hypophosphataemia | | |
| subjects affected / exposed | 122 / 287 (42.51%) | 122 / 288 (42.36%) |
| occurrences (all) | 133 | 133 |
| Metabolic acidosis | | |
| subjects affected / exposed | 60 / 287 (20.91%) | 50 / 288 (17.36%) |
| occurrences (all) | 70 | 57 |
| Vitamin D deficiency | | |
| subjects affected / exposed | 35 / 287 (12.20%) | 38 / 288 (13.19%) |
| occurrences (all) | 35 | 38 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|---|
| 06 October 2017 | The changes included: 1) The objectives involving results from kidney biopsies were modified. The first secondary objective was changed to an exploratory objective. An additional exploratory objective was added to compare outcomes at centers that routinely performed maintenance biopsies with those that did not. 2) An exploratory objective was changed to the first secondary objective. 3) The sub-categories for the molecular profiling endpoints were revised. To accommodate these changes, additional creatinine measurements were recorded to distinguish between clinical acute rejection and subacute rejection, the recording of additional creatinine results (from SOC testing) was also added. 4) The planned number of centers was increased from 25 to 30. 5) The upper age limit for study eligibility was increased from 65 to 70 years. 6) Study-specific instructions for nonoral administration of tacrolimus were added. 7) The inclusion criterion requiring the most recent pretransplant calculated panel reactive antibody (cPRA) $\leq 50\%$ was removed. 8) The exclusion criteria regarding crossmatches and anti-HLA antibody testing results (exclusion criteria 11 to 13) were reorganized for clarity. 9) Undergoing a second organ transplant was added as a discontinuation criterion. 10) After 6 weeks posttransplant had elapsed, removal of a minimum tacrolimus trough concentration requirement from the discontinuation criteria. 11) The FAS was modified to include all randomized subjects who receive at least one dose of study drug. An additional analysis set, the mFAS, was designated as the primary analysis set for efficacy assessments. This set is defined as including all randomized subjects who: 1) receive at least one dose of study drug and 2) are not deemed by the adjudication board to have pre-formed DSA. |
| 06 October 2017 | The changes included: 12) For the study visits between Day 90 and Day 365 only, all available outpatient tacrolimus concentration assessments done per standard of care and available in the centralized medical records will be recorded. 13) For subjects who develop clinically significant BK viremia (as assessed per standard of care) during study participation, the peak viremia level obtained per standard of care will be retrospectively recorded in the eCRF at the time of the subject's discontinuation or completion. 14) The scope of the MFI Adjudication Board broadened. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported