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
Randomized but Never Received Study Drug	12	12
Protocol deviation	20	23
Miscellaneous	5	6
Lack of efficacy	4	3
Adverse event, serious fatal	2	2
Adverse event, non-fatal	48	40
Consent withdrawn by subject	4	8
Lost to follow-up	1	7

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

	DSA Immunoglobulin G (IgG3) Isotype

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 paticipants 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/1.73m^2)

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/1.73m^2

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/1.73m^2

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 paticipants 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 paticipants	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	
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	0 / 0	0 / 1	

treatment / all			
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	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	
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	
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	
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	
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	
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	
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	
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	
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	
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	
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	
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	
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	
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	
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	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	31 / 287 (10.80%)	26 / 288 (9.03%)	
occurrences causally related to	18 / 36	12 / 33	

treatment / all			
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	
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	
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	
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	
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	
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	
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	1 / 4	2 / 4	

treatment / all			
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	

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	45 / 287 (15.68%)	41 / 288 (14.24%)	
occurrences (all)	51	44	
Orthostatic hypotension			
subjects affected / exposed	19 / 287 (6.62%)	13 / 288 (4.51%)	
occurrences (all)	20	14	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	14 / 287 (4.88%)	21 / 288 (7.29%)	
occurrences (all)	15	23	
Fatigue			
subjects affected / exposed	45 / 287 (15.68%)	45 / 288 (15.63%)	
occurrences (all)	51	48	
Chest pain			
subjects affected / exposed	12 / 287 (4.18%)	15 / 288 (5.21%)	
occurrences (all)	12	15	
Oedema peripheral			
subjects affected / exposed	53 / 287 (18.47%)	53 / 288 (18.40%)	
occurrences (all)	64	63	
Oedema			
subjects affected / exposed	17 / 287 (5.92%)	10 / 288 (3.47%)	
occurrences (all)	18	12	

Pyrexia			
subjects affected / exposed	38 / 287 (13.24%)	28 / 288 (9.72%)	
occurrences (all)	44	37	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	24 / 287 (8.36%)	12 / 288 (4.17%)	
occurrences (all)	29	14	
Insomnia			
subjects affected / exposed	44 / 287 (15.33%)	40 / 288 (13.89%)	
occurrences (all)	47	42	
Injury, poisoning and procedural complications			
Delayed graft function			
subjects affected / exposed	30 / 287 (10.45%)	15 / 288 (5.21%)	
occurrences (all)	30	15	
Incision site pain			
subjects affected / exposed	47 / 287 (16.38%)	24 / 288 (8.33%)	
occurrences (all)	50	25	
Procedural pain			
subjects affected / exposed	91 / 287 (31.71%)	55 / 288 (19.10%)	
occurrences (all)	105	62	
Investigations			
Blood creatinine increased			
subjects affected / exposed	43 / 287 (14.98%)	37 / 288 (12.85%)	
occurrences (all)	49	40	
Viral test positive			
subjects affected / exposed	18 / 287 (6.27%)	10 / 288 (3.47%)	
occurrences (all)	18	11	
Weight increased			
subjects affected / exposed	14 / 287 (4.88%)	16 / 288 (5.56%)	
occurrences (all)	14	18	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	24 / 287 (8.36%)	27 / 288 (9.38%)	
occurrences (all)	25	28	
Blood and lymphatic system disorders			

Leukocytosis			
subjects affected / exposed	21 / 287 (7.32%)	12 / 288 (4.17%)	
occurrences (all)	23	12	
Anaemia			
subjects affected / exposed	37 / 287 (12.89%)	42 / 288 (14.58%)	
occurrences (all)	45	46	
Neutropenia			
subjects affected / exposed	28 / 287 (9.76%)	20 / 288 (6.94%)	
occurrences (all)	30	23	
Leukopenia			
subjects affected / exposed	58 / 287 (20.21%)	66 / 288 (22.92%)	
occurrences (all)	67	74	
Thrombocytopenia			
subjects affected / exposed	18 / 287 (6.27%)	14 / 288 (4.86%)	
occurrences (all)	18	14	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	20 / 287 (6.97%)	26 / 288 (9.03%)	
occurrences (all)	22	26	
Dyspnoea			
subjects affected / exposed	30 / 287 (10.45%)	32 / 288 (11.11%)	
occurrences (all)	38	34	
Oropharyngeal pain			
subjects affected / exposed	21 / 287 (7.32%)	23 / 288 (7.99%)	
occurrences (all)	22	27	
Nervous system disorders			
Dizziness			
subjects affected / exposed	30 / 287 (10.45%)	34 / 288 (11.81%)	
occurrences (all)	36	41	
Headache			
subjects affected / exposed	38 / 287 (13.24%)	46 / 288 (15.97%)	
occurrences (all)	43	58	
Tremor			
subjects affected / exposed	84 / 287 (29.27%)	94 / 288 (32.64%)	
occurrences (all)	89	99	
Gastrointestinal disorders			

Abdominal distension			
subjects affected / exposed	21 / 287 (7.32%)	14 / 288 (4.86%)	
occurrences (all)	27	15	
Abdominal pain			
subjects affected / exposed	35 / 287 (12.20%)	31 / 288 (10.76%)	
occurrences (all)	39	34	
Constipation			
subjects affected / exposed	100 / 287 (34.84%)	90 / 288 (31.25%)	
occurrences (all)	113	101	
Diarrhoea			
subjects affected / exposed	115 / 287 (40.07%)	128 / 288 (44.44%)	
occurrences (all)	160	165	
Dyspepsia			
subjects affected / exposed	24 / 287 (8.36%)	24 / 288 (8.33%)	
occurrences (all)	29	26	
Nausea			
subjects affected / exposed	104 / 287 (36.24%)	101 / 288 (35.07%)	
occurrences (all)	133	131	
Gastrooesophageal reflux disease			
subjects affected / exposed	9 / 287 (3.14%)	15 / 288 (5.21%)	
occurrences (all)	9	18	
Vomiting			
subjects affected / exposed	61 / 287 (21.25%)	41 / 288 (14.24%)	
occurrences (all)	77	54	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	21 / 287 (7.32%)	27 / 288 (9.38%)	
occurrences (all)	23	30	
Haematuria			
subjects affected / exposed	30 / 287 (10.45%)	25 / 288 (8.68%)	
occurrences (all)	30	26	
Proteinuria			
subjects affected / exposed	15 / 287 (5.23%)	5 / 288 (1.74%)	
occurrences (all)	15	5	
Urinary retention			
subjects affected / exposed	18 / 287 (6.27%)	13 / 288 (4.51%)	

occurrences (all)	18	14	

Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	21 / 287 (7.32%)	18 / 288 (6.25%)	
occurrences (all)	23	18	
Alopecia			
subjects affected / exposed	15 / 287 (5.23%)	24 / 288 (8.33%)	
occurrences (all)	15	24	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	17 / 287 (5.92%)	19 / 288 (6.60%)	
occurrences (all)	17	20	
Arthralgia			
subjects affected / exposed	16 / 287 (5.57%)	14 / 288 (4.86%)	
occurrences (all)	22	18	
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	
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	
Hypocalcaemia			
subjects affected / exposed	41 / 287 (14.29%)	37 / 288 (12.85%)	
occurrences (all)	42	43	
Hyperphosphataemia			
subjects affected / exposed	21 / 287 (7.32%)	18 / 288 (6.25%)	
occurrences (all)	22	20	
Hypokalaemia			
subjects affected / exposed	37 / 287 (12.89%)	38 / 288 (13.19%)	
occurrences (all)	44	39	
Hypoglycaemia			
subjects affected / exposed	16 / 287 (5.57%)	12 / 288 (4.17%)	
occurrences (all)	20	14	
Hyponatraemia			
subjects affected / exposed	18 / 287 (6.27%)	19 / 288 (6.60%)	
occurrences (all)	18	21	
Hypomagnesaemia			
subjects affected / exposed	124 / 287 (43.21%)	124 / 288 (43.06%)	
occurrences (all)	143	142	
Hypophosphataemia			
subjects affected / exposed	122 / 287 (42.51%)	122 / 288 (42.36%)	
occurrences (all)	133	133	
Vitamin D deficiency			
subjects affected / exposed	35 / 287 (12.20%)	38 / 288 (13.19%)	
occurrences (all)	35	38	
Metabolic acidosis			
subjects affected / exposed	60 / 287 (20.91%)	50 / 288 (17.36%)	
occurrences (all)	70	57	
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	
Upper respiratory tract infection			
subjects affected / exposed	31 / 287 (10.80%)	25 / 288 (8.68%)	
occurrences (all)	32	27	
Nasopharyngitis			
subjects affected / exposed	17 / 287 (5.92%)	21 / 288 (7.29%)	
occurrences (all)	19	23	
Urinary tract infection			
subjects affected / exposed	44 / 287 (15.33%)	50 / 288 (17.36%)	
occurrences (all)	77	65	

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) ≤ 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