Clinical trial results:
MULTICENTRE, OPEN LABEL, RANDOMIZED, TWO-ARM, PARALLEL-GROUP STUDY TO ASSESS EFFICACY AND SAFETY OF ENVARSUS® COMPARED WITH TACROLIMUS USED AS PER CURRENT CLINICAL PRACTICE IN THE INITIAL MAINTENANCE SETTING IN DE NOVO KIDNEY TRANSPLANT PATIENTS.

Summary

EudraCT number	2014-004314-29
Trial protocol	BE AT ES DE PL IT
Global end of trial date	24 January 2017

Results information

Result version number	v1 (current)
This version publication date	02 February 2018
First version publication date	02 February 2018

Trial information

Trial identification

Sponsor protocol code	CCD-06235AA1-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02432833
WHO universal trial number (UTN)	-
Other trial identifiers	N/A: N/A

Notes:

Sponsors

Sponsor organisation name	Chiesi Farmaceutici S.p.A.
Sponsor organisation address	Via Palermo 26/A, Parma, Italy,
Public contact	Clinical Trial Trasparency, Clinical Trial Trasparency, clinicaltrials_info@chiesi.com
Scientific contact	Clinical Trial Trasparency, Clinical Trial Trasparency, clinicaltrials_info@chiesi.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	27 November 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 January 2017
Global end of trial reached?	Yes
Global end of trial date	24 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare tacrolimus dosing of the new Envarsus®-based immunosuppressive regimen with current clinical practice over 6 months following de novo renal transplantation in a real-life setting in different European Countries.

Protection of trial subjects:

The study proposal was submitted to the Independent Ethics Committee (IEC) in accordance with the requirements of each country, and the IEC provided opinion in writing.
The study was conducted in accordance with the Declaration of Helsinki, the International Council for Harmonisation of Good Clinical Practice guidelines, and followed all other requirements of local laws.
The consent document met all applicable local laws and provided the patient with information regarding the purpose, procedures, requirements and restrictions of the study, along with any known risks and potential benefits associated with the investigational product and the established provisions for maintaining the confidentiality of personal information. The Investigator obtained written consent from each subject or from the subject's legal representative prior to any study related procedures taking place.

Background therapy:

Envarsus® is a prolonged release formulation of tacrolimus developed utilising a MeltDose™ drug-delivery technology which increases the bioavailability of poorly water soluble compounds. The improved bioavailability of Envarsus, which allows a QD administration, determines lower inter- and intra subject variability of drug absorption with reduced peak-to-trough fluctuation and earlier achievement of a stable tacrolimus profile, as shown in healthy volunteers .

Evidence for comparator:

Despite the proven immunosuppressive efficacy of tacrolimus, currently marketed formulations such as Prograf® and Advagraf exhibit limitations, primarily in terms of PK properties and tolerability.
Prograf and Advagraf exhibit significant inter- and intra individual variability in absorption because of the interactions with both food and concomitant medications, and metabolism through the cytochrome P-450 system which is subject to functional polymorphisms. In addition, both Prograf and Advagraf exhibit a very low bioavailability due to poor water solubility and pre systemic gastrointestinal (GI) metabolism.

Actual start date of recruitment	16 May 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Norway: 5
Country: Number of subjects enrolled	Poland: 30
Country: Number of subjects enrolled	Spain: 102
Country: Number of subjects enrolled	Sweden: 5
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	Austria: 18

Country: Number of subjects enrolled	Belgium: 20
Country: Number of subjects enrolled	France: 113
Country: Number of subjects enrolled	Germany: 51
Country: Number of subjects enrolled	Italy: 76
Worldwide total number of subjects	428
EEA total number of subjects	428

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)	310
From 65 to 84 years	118
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted in 51 active sites out of 65 open sites, located in 10 European countries. Patient were recruited in the following 51 active sites: Austria (2 sites), Belgium (2 sites), France (11 sites), Germany (7 sites), Italy (10 sites), Norway (1 site), Poland (2 sites), Spain (11 sites), Sweden (2 sites) and UK (3 sites).

Pre-assignment

Screening details:

A screening visit (Visit 1) was performed from 0 to 28 days prior to kidney transplantation when feasible. The screening visit (Visit 1) could be combined with Visit 2 if all information was already available to the Investigators for the inclusion and exclusion criteria evaluation at the time of randomization.

Pre-assignment period milestones

Number of subjects started	428
Number of subjects completed	403

Pre-assignment subject non-completion reasons

Reason: Number of subjects	other: 12
Reason: Number of subjects	no met inclusion criteria/exclusion criteria: 10
Reason: Number of subjects	Adverse event, non-fatal: 2
Reason: Number of subjects	Protocol deviation: 1

Period 1

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

Blinding implementation details:

N.A

Arms

Are arms mutually exclusive?	Yes
Arm title	1_Envarsus®

Arm description:

Active Treatment Arm with Envarsus tablets: randomization 1:1 ratio (Arm1: Arm2). Active substance: Tacrolimus monohydrate.
Oral administration once daily.
starting dose: 0.17mg/kg/day
Whatever the treatment, patients will have their dose adjusted to maintain tacrolimus whole blood trough levels within the standard reference ranges of 5-15 ng/ml in the first three months after transplantation and 5-10 ng/ml afterwards.

Arm type	Experimental
Investigational medicinal product name	Envarsus®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Envarsus® Oval, white to off-white uncoated tablets will be administered orally once daily in the morning. The treatment should commence at the starting dose of 0.17 mg/kg/day.
Whatever the treatment, patients will have their dose adjusted to maintain tacrolimus whole blood trough levels within the standard reference ranges of 5-15 ng/ml in the first three months after transplantation and 5-10 ng/ml afterwards.

Arm title	2_Prograf® /Advagraf®

Arm description:

Reference therapy arm (Arm2) with randomization 1:1 ratio (Arm1: Arm2) (active substance: Tacrolimus monohydrate)
- Prograf® capsules will be administered orally. The treatment should commence at the starting total daily dose of 0.2 mg/kg/day delivered in two equally divided doses 12 hours apart (one in the morning and one in the evening) or
- Advagraf® capsules will be administered orally. The treatment should commence at the starting total daily dose of 0.2 mg/kg/day administered once daily in the morning.
Whatever the treatment, patients will have their dose adjusted to maintain tacrolimus whole blood trough levels within the standard reference ranges of 5-15 ng/ml in the first three months after transplantation and 5-10 ng/ml afterwards.

Arm type	Active comparator
Investigational medicinal product name	Prograf®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Prograf are hard capsules for oral formulation provided in 0.5 mg, 1.0 mg and 5.0 mg dosage strengths,administered twice daily.
The treatment should commence at the starting total daily dose of 0.2 mg/kg/day delivered in two equally divided doses 12 hours apart (one in the morning and one in the evening).

Investigational medicinal product name	Advagraf®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Prolonged-release capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Advagraf are prolonged-release hard capsules for oral formulation provided in 0.5 mg, 1.0 mg, 3.0 mg and 5.0 mg dosage strengths,administered once daily.
The treatment should commence at the starting total daily dose of 0.2 mg/kg/day administered once daily in the morning.

Number of subjects in period 1[1]	1_Envarsus®	2_Prograf® /Advagraf®
Started	201	202
Completed	177	173
Not completed	24	29
Adverse event, serious fatal	2	3
Consent withdrawn by subject	5	3
Adverse event, non-fatal	11	13
no met inclusion criteria/exclusion criteria	1	3

other	3	2
Protocol deviation	2	2
Lack of efficacy	-	3

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: In the study were enrolled 428 subject, yet 25 of these didn't attend the randomization visit for the reason described i the "Pre-assignment subject non-completion reasons".
The baseline period was considered as the number of patients that attend the Randomization visit (day 0)

Baseline characteristics

Reporting groups

Reporting group title	1_Envarsus®

Reporting group description:

Active Treatment Arm with Envarsus tablets: randomization 1:1 ratio (Arm1: Arm2). Active substance: Tacrolimus monohydrate.
Oral administration once daily.
starting dose: 0.17mg/kg/day
Whatever the treatment, patients will have their dose adjusted to maintain tacrolimus whole blood trough levels within the standard reference ranges of 5-15 ng/ml in the first three months after transplantation and 5-10 ng/ml afterwards.

Reporting group title	2_Prograf® /Advagraf®

Reporting group description:

Reference therapy arm (Arm2) with randomization 1:1 ratio (Arm1: Arm2) (active substance: Tacrolimus monohydrate)
- Prograf® capsules will be administered orally. The treatment should commence at the starting total daily dose of 0.2 mg/kg/day delivered in two equally divided doses 12 hours apart (one in the morning and one in the evening) or
- Advagraf® capsules will be administered orally. The treatment should commence at the starting total daily dose of 0.2 mg/kg/day administered once daily in the morning.
Whatever the treatment, patients will have their dose adjusted to maintain tacrolimus whole blood trough levels within the standard reference ranges of 5-15 ng/ml in the first three months after transplantation and 5-10 ng/ml afterwards.

Reporting group values	1_Envarsus®	2_Prograf® /Advagraf®	Total
Number of subjects	201	202	403
Age categorical			
adult male or female of at least 18 years			
Units: Subjects			
Adults (18-64 years)	148	147	295
From 65-84 years	53	55	108
Age continuous			
Units: years			
arithmetic mean	53.7	54.9	
standard deviation	± 14.2	± 14.2	-
Gender categorical			
Units: Subjects			
Female	55	65	120
Male	146	137	283
Race			
White, Asian, Black and other races. Results reported in table 14.1.2.1 of Clinical Study Report			
Units: Subjects			
White	196	193	389
Asian	2	3	5
Black	1	1	2
other	2	5	7

End points

End points reporting groups

Reporting group title	1_Envarsus®

Reporting group description:

Active Treatment Arm with Envarsus tablets: randomization 1:1 ratio (Arm1: Arm2). Active substance: Tacrolimus monohydrate.
Oral administration once daily.
starting dose: 0.17mg/kg/day
Whatever the treatment, patients will have their dose adjusted to maintain tacrolimus whole blood trough levels within the standard reference ranges of 5-15 ng/ml in the first three months after transplantation and 5-10 ng/ml afterwards.

Reporting group title	2_Prograf® /Advagraf®

Reporting group description:

Reference therapy arm (Arm2) with randomization 1:1 ratio (Arm1: Arm2) (active substance: Tacrolimus monohydrate)
- Prograf® capsules will be administered orally. The treatment should commence at the starting total daily dose of 0.2 mg/kg/day delivered in two equally divided doses 12 hours apart (one in the morning and one in the evening) or
- Advagraf® capsules will be administered orally. The treatment should commence at the starting total daily dose of 0.2 mg/kg/day administered once daily in the morning.
Whatever the treatment, patients will have their dose adjusted to maintain tacrolimus whole blood trough levels within the standard reference ranges of 5-15 ng/ml in the first three months after transplantation and 5-10 ng/ml afterwards.

Primary: 1_Tacrolimus Total Daily Dose (TTD) from Week 3 to Month 6

End point title	1_Tacrolimus Total Daily Dose (TTD) from Week 3 to Month 6

End point description:

The primary efficacy endpoint was the tacrolimus Total Daily Dose from Week 3 (Visit 9) to Month 6 (Visit 15). Results from week 3 to month 6 have been reported.

Shown are the number of patients included in the model (modified Intention-to-treat [mITT] population [N]; patients with available results [n]

End point type	Primary

End point timeframe:

from Week 3 (Visit 9) to Month 6 (Visit 15).

End point values	1_Envarsus®	2_Prograf® /Advagraf®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	191[1]	194[2]		
Units: milligram(s)				
arithmetic mean (standard deviation)	5.165 (± 2.970)	6.280 (± 3.557)		

Notes:

[1] - N=200
n=191
[2] - N=201
n=194

Statistical analyses

Statistical analysis title	1_Average Tacrolimus TDD from week 3 to month 6

Statistical analysis description:

Primary efficacy analysis.
The average tacrolimus TDD from Week 3 (Visit 9) to Month 6 (Visit 15) will be compared between the two groups (Envarsus vs Prograf/Advagraf) using an ANOVA model.

Comparison groups	1_Envarsus® v 2_Prograf® /Advagraf®
Number of subjects included in analysis	385
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	< 0.001
Method	ANOVA
Parameter estimate	LS Mean difference
Point estimate	-1.108
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.764
upper limit	-0.452

Notes:

[3] - An analysis of variance (ANOVA) model was performed with treatment group and country as fixed effects. The adjusted means in each treatment group and the adjusted mean difference between treatment groups were displayed with the corresponding 2-sided 95% CI.

Secondary: 2_Ratio between TL and TDD

End point title	2_Ratio between TL and TDD

End point description:

Efficacy endpoint.
The ratio between trough levels and total daily dose was analysed, as it is an indicator of drug bioavailability. For each subject at each time point, the TL/TDD ratio was calculated as follows: TL (time t+1) / TDD (t).
Shown are the number of patients included in the model (modified Intention-to-treat [mITT] population [N]; patients with available results [n]).

End point type	Secondary

End point timeframe:

The ratios were calculated at visit, by period (including Week 3 to Month 6) and overall: results from Week 3 to Month 6 were reported.

End point values	1_Envarsus®	2_Prograf® /Advagraf®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	191[4]	194[5]		
Units: ng/mL/mg				
arithmetic mean (standard deviation)				
week 3-month 6	2.262 (± 1.375)	1.692 (± 0.854)		

Notes:

[4] - N=200; n=191

[5] - N=201;n=194

Statistical analyses

Statistical analysis title	1_Ratio between TL and TDD

Statistical analysis description:

Average ratio is the average of all ratios TL (time t+1) / TDD (t) measured during the time period. For the period Week 3 to Month 6 (Study Day 21 to last assessment), the ratio was analysed using an ANOVA model.

Comparison groups	1_Envarsus® v 2_Prograf® /Advagraf®
Number of subjects included in analysis	385
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	< 0.001
Method	ANOVA
Parameter estimate	LS Mean difference
Point estimate	0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.342
upper limit	0.799

Notes:

[6] - ANOVA model have been constructed with treatment arm and country as fixed effects. The adjusted means in each treatment arm and the adjusted mean difference between treatment arms have been displayed with the corresponding two-sided 95 % CI.

Secondary: 3_Treatment failure rate

End point title	3_Treatment failure rate

End point description:

Efficacy endpoint.
Treatment failure rate, a composite endpoint, includes any patient who experienced within 6 months after randomization any of the following: death, graft failure, BPAR (biopsy-proven acute rejection) or lost to follow-up. Overall results have been reported.
Shown are the number of patients included in the model (modified Intention-to-treat [mITT] population [N]; patients with available results [n]).

End point type	Secondary

End point timeframe:

within 6 months after randomization.

End point values	1_Envarsus®	2_Prograf® /Advagraf®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	200[7]	201[8]		
Units: percentage of subject (0-100%)				
overall_death	2	2		
overall_graft failure	2	2		
overall_BPAR	6	5		
overall_lost on Follow Up	0	0		
overall_treatment failure	9	9		

Notes:

[7] - N=200;n=200

[8] - N=201;n=201

Statistical analyses

Statistical analysis title	1_Treatment Failure Rate_overall_treatment Failure

Statistical analysis description:

A Fisher’s exact test has been used to estimate the difference between treatments for the entire study period.

Comparison groups	2_Prograf® /Advagraf® v 1_Envarsus®
Number of subjects included in analysis	401
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.999 [9]
Method	Fisher exact
Parameter estimate	difference between proportions
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.7
upper limit	5.8

Notes:

[9] - P-value was based on a 2-sided Fisher's exact test to evaluate the difference between treatment groups. The 95 % CI for the difference in proportions between the two treatment arms based on the Newcombe-Wilson method

Statistical analysis title	2_Treatment Failure Rate_overall_death

Statistical analysis description:

A Fisher’s exact test has been used to estimate the difference between treatments for the entire study period.

Comparison groups	1_Envarsus® v 2_Prograf® /Advagraf®
Number of subjects included in analysis	401
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.999 [10]
Method	Fisher exact
Parameter estimate	LS Mean difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2
upper limit	3.3

Notes:

[10] - P-value was based on a 2-sided Fisher's exact test to evaluate the difference between treatment groups. The 95 % CI for the difference in proportions between the two treatment arms based on the Newcombe-Wilson method

Statistical analysis title	3_Treatment Failure Rate_overall_graft failure

Statistical analysis description:

A Fisher’s exact test has been used to estimate the difference between treatments for the entire study period.

Comparison groups	1_Envarsus® v 2_Prograf® /Advagraf®

Number of subjects included in analysis	401
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.999 [11]
Method	Fisher exact
Parameter estimate	LS Mean difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2
upper limit	3.3

Notes:

[11] - P-value was based on a 2-sided Fisher's exact test to evaluate the difference between treatment groups. The 95 % CI for the difference in proportions between the two treatment arms based on the Newcombe-Wilson method

Statistical analysis title	4_Treatment Failure Rate_overall_BPAR

Statistical analysis description:

A Fisher’s exact test has been used to estimate the difference between treatments for the entire study period.

Comparison groups	1_Envarsus® v 2_Prograf® /Advagraf®
Number of subjects included in analysis	401
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.688 [12]
Method	Fisher exact
Parameter estimate	LS Mean difference
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.7
upper limit	5.8

Notes:

[12] - P-value was based on a 2-sided Fisher's exact test to evaluate the difference between treatment groups. The 95 % CI for the difference in proportions between the two treatment arms based on the Newcombe-Wilson method

Secondary: 4_Time to treatment failure

End point title	4_Time to treatment failure

End point description:

Efficacy endpoint.
Time to treatment failure is determined by the first episode of death, graft failure, BPAR or lost to follow-up, whichever occurs first. Time to treatment failure (days) will be calculated as difference between the date of event and the date of randomization + 1. Patients who prematurely withdraw from the study for any other reason (without experiencing one of the four events) will be right-censored for this analysis at the time of discontinuation. Patients who complete the study without experiencing any of the four events will be right censored at last dose.
Shown are the number of patients included in the model (modified Intention-to-treat [mITT] population [N]; patients with available results [n])

End point type	Secondary

End point timeframe:

from the randomization day +1.

End point values	1_Envarsus®	2_Prograf® /Advagraf®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	200[13]	201[14]		
Units: percentage of subjects (0-100%)				
subjects event	9	9		
subjects censored	91	91		

Notes:

[13] - N=200;n=200

[14] - N=201;n=201

Statistical analyses

Statistical analysis title	1_Time to treatment failure
Statistical analysis description: the ratio was calculated as Envaruss/ Prograf/advagraf.	
Comparison groups	1_Envarsus® v 2_Prograf® /Advagraf®
Number of subjects included in analysis	401
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.965
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	1.23

Secondary: 5_Proportion of patients with delayed graft function

End point title	5_Proportion of patients with delayed graft function
End point description: Efficacy endpoint. Proportion of patients with delayed graft function (defined as dialysis in the first week) will be presented by treatment group. Difference between treatments will be evaluated using a Fisher exact test at the 0.05 significant level. The 95% CI for the treatments difference will be also computed. Number of subjects with delayed graft function was below presented. Shown are the number of patients included in the model (modified Intention-to-treat [mITT] population [N]; patients with available results [n])	
End point type	Secondary
End point timeframe: overall the study.	

End point values	1_Envarsus®	2_Prograf® /Advagraf®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	200[15]	201[16]		
Units: number of subjects	23	22		

Notes:

[15] - N=200;n=200

[16] - N=201;n=201

Statistical analyses

Statistical analysis title	1_delayed graft function

Statistical analysis description:

A Fisher’s exact test has been used to estimate the difference between treatments.

Comparison groups	1_Envarsus® v 2_Prograf® /Advagraf®
Number of subjects included in analysis	401
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.876 [17]
Method	Fisher exact
Parameter estimate	difference between proportions
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.7
upper limit	6.9

Notes:

[17] - P-value was based on a 2-sided Fisher's exact test to evaluate the difference between treatment groups. The 95 % CI for the difference in proportions between the two treatment arms based on the Newcombe-Wilson method.

Secondary: 6_Proportion of patients with local diagnosis of acute rejection requiring treatment

End point title	6_Proportion of patients with local diagnosis of acute rejection requiring treatment

End point description:

Efficacy endpoint.
Proportion of patients with local diagnosis of acute rejection requiring treatment will be presented by treatment group. Difference between treatments will be evaluated using a Fisher’s exact test at the 0.05 significant level. The 95% CI for the treatments difference will be also computed.
Number of patients with local diagnosis of acute rejection requiring treatment was below presented.
Shown are the number of patients included in the model (modified Intention-to-treat [mITT] population [N]; patients with available results [n])

End point type	Secondary

End point timeframe:

overall the study

End point values	1_Envarsus®	2_Prograf® /Advagraf®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	200[18]	201[19]		
Units: number of subjects	7	6		

Notes:

[18] - N=200;n=200

[19] - N=201;n=201

Statistical analyses

Statistical analysis title	1_Local diagnosis Acute Rejection requiring treat.

Statistical analysis description:

A Fisher's exact test has been used to estimate the difference between treatments.

Comparison groups	1_Envarsus® v 2_Prograf® /Advagraf®
Number of subjects included in analysis	401
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.787 [20]
Method	Fisher exact
Parameter estimate	difference between proportions
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.3
upper limit	4.4

Notes:

[20] - P-value was based on a 2-sided Fisher's exact test to evaluate the difference between treatment groups. The 95 % CI for the difference in proportions between the two treatment arms based on the Newcombe-Wilson method.

Secondary: 7_Post-transplant diabetes mellitus (PTDM)

End point title	7_Post-transplant diabetes mellitus (PTDM)

End point description:

Safety endpoint.
Diabetes was assessed through measurement of fasting plasma glucose (FPG), HbA1C and the need for hypoglycaemic agents (oral or insulin). Post-transplant diabetes mellitus was defined by the need for any antidiabetic agent (oral or insulin) and/or HbA1c >6.5% at Months 3 and 6 in a subject with no prior medical history of diabetes before transplantation.
Shown are the number of patients included in the model (safety population [N]; patients with available results [n])

N°of subject analysed (n) at month 3 and month 6 are the number of subject with no prior medical history of diabetes before transplantation having laboratory value at a particular visit.

End point type	Secondary

End point timeframe:

Months 3 and 6

End point values	1_Envarsus®	2_Prograf® /Advagraf®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	200[21]	201[22]		
Units: number of subjects				
month 3	23	32		
month 6	23	25		

Notes:

[21] - N=200
N°of subj with no prior medical history of diabetes :
n month 3: 115
n month 6:129
[22] - N=200
N°of subj with no prior medical history of diabetes :
n month 3: 126
n month 6:125

Statistical analyses

Statistical analysis title	1_PTDM_month 3

Statistical analysis description:

A Fisher’s exact test will be used to estimate the difference between treatments.
n° of subjects included in this statistical analysis (n) is:
n Envarsus=115 out of 200
n Prograf/Advagraf=126 out of 201
total number = 241 out of 401

Comparison groups	1_Envarsus® v 2_Prograf® /Advagraf®
Number of subjects included in analysis	401
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.214 [23]
Method	Fisher exact
Parameter estimate	Percentage difference
Point estimate	-7.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.3
upper limit	3.4

Notes:

[23] - P-value was based on a 2-sided Fisher's exact test

Statistical analysis title	2_PTDM_month 6

Statistical analysis description:

A Fisher’s exact test will be used to estimate the difference between treatments.
n° of subjects included in this statistical analysis (n) is:
n Envarsus=129 out of 200
n Prograf/Advagraf=125 out of 201
total number = 254 out of 401

Comparison groups	1_Envarsus® v 2_Prograf® /Advagraf®

Number of subjects included in analysis	401
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.749 [24]
Method	Fisher exact
Parameter estimate	Percentage difference
Point estimate	-2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.8
upper limit	7.5

Notes:

[24] - P-value was based on a 2-sided Fisher's exact test.

Secondary: 8_post-transplant hyperglycaemia (PTH)

End point title	8_post-transplant hyperglycaemia (PTH)

End point description:

Safety endpoint.
Diabetes was assessed through measurement of fasting plasma glucose (FPG), HbA1C and the need for hypoglycaemic agents (oral or insulin). PTH would be defined by a FPG ≥126 mg/dL, and/or for subjects with no prior medical history of diabetes, an afternoon capillary glucose level of ≥200 mg/dL with or without insulin requirement or need for an oral hypoglycaemic agent
Shown are the number of patients included in the model (safety population [N]; patients with available results [n])
N°of subject analysed at month 3 and month 6 are the number of subject with no prior medical history of diabetes before transplantation having laboratory value at a particular visit.

End point type	Secondary

End point timeframe:

Months 3 and 6

End point values	1_Envarsus®	2_Prograf® /Advagraf®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	200[25]	201[26]		
Units: number of subjects				
month 3	14	31		
month 6	14	25		

Notes:

[25] - N=200
N°of subj with no prior medical history of diabetes :
n month 3: 155
n month 6:152
[26] - N=201
N°of subj with no prior medical history of diabetes :
n month 3: 157
n month 6:150

Statistical analyses

Statistical analysis title	1_PTH_month 3

Statistical analysis description:

A Fisher’s exact test will be used to estimate the difference between treatments

n° of subjects included in this statistical analysis (n) is:
n Envarsus=155 out of 200
n Prograf/Advagraf=157 out of 201
total number = 312 out of 401

Comparison groups	1_Envarsus® v 2_Prograf® /Advagraf®
Number of subjects included in analysis	401
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.009 [27]
Method	Fisher exact
Parameter estimate	Percentage difference
Point estimate	-10.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.5
upper limit	-2.9

Notes:

[27] - P-value was based on a 2-sided Fisher's exact test

Statistical analysis title	2_PTH_month 6

Statistical analysis description:

A Fisher’s exact test will be used to estimate the difference between treatments.
n° of subjects included in this statistical analysis (n) is:
n Envarsus=152 out of 200
n Prograf/Advagraf=150 out of 201
total number = 302 out of 401

Comparison groups	1_Envarsus® v 2_Prograf® /Advagraf®
Number of subjects included in analysis	401
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.06 [28]
Method	Fisher exact
Parameter estimate	Percentage difference
Point estimate	-7.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.2
upper limit	0.2

Notes:

[28] - P-value was based on a 2-sided Fisher's exact

Secondary: 9_Glycated hemoglobin (HbA1c)

End point title	9_Glycated hemoglobin (HbA1c)

End point description:

Safety endpoint.
Glycated hemoglobin (HbA1c).chnages from baseline of HbA1c (%) at day 90 and day 180 have been reported.
Shown are the number of patients included in the model (safety population [N]; patients with available results [n])

End point type	Secondary

End point timeframe:
Months 3 and 6

End point values	1_Envarsus®	2_Prograf® /Advagraf®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	200[29]	201[30]		
Units: percent				
arithmetic mean (standard deviation)				
change from baseline_day 90	0.42 (± 0.84)	0.54 (± 0.95)		
change from baseline_day 180	0.36 (± 0.82)	0.58 (± 0.84)		

Notes:

[29] - N=200
n day 90= 102
n day 180= 109
[30] - N=201
n day 90= 109
n day 180= 112

Statistical analyses

Statistical analysis title	1_HbA1c_day 90

Statistical analysis description:

HbA1c at Visit 12 (Month 3) has been analysed using an ANCOVA model.The ANCOVA model utilised at each selected post-baseline visit includes treatment and country as fixed effects, and baseline HbA1C value as covariate.
n° of subjects included in this statistical analysis (n) is:
n Envarsus=102 out of 200
n Prograf/Advagraf=109 out of 201
total number = 211 out of 401

Comparison groups	1_Envarsus® v 2_Prograf® /Advagraf®
Number of subjects included in analysis	401
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.287
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-0.125
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.356
upper limit	0.106

Statistical analysis title	2_Hb1Ac_day 180

Statistical analysis description:

HbA1c at Visit 15 (Month 6) has been analysed using an ANCOVA model.The ANCOVA model utilised at each selected post-baseline visit includes treatment and country as fixed effects, and baseline HbA1C value as covariate
n° of subjects included in this statistical analysis (n) is:
n Envarsus=109 out of 200

n Prograf/Advagraf=112 out of 201
total number = 221 out of 401

Comparison groups	1_Envarsus® v 2_Prograf® /Advagraf®
Number of subjects included in analysis	401
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.025
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-0.243
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.455
upper limit	-0.031

Secondary: 10_Tacrolimus Total Daily Dose

End point title	10_Tacrolimus Total Daily Dose

End point description:

Efficacy endpoint.
Shown are the number of patients included in the model (modified Intention-to-treat [mITT] population [N]; patients with available results [n])

End point type	Secondary

End point timeframe:

overall study

End point values	1_Envarsus®	2_Prograf® /Advagraf®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	200[31]	201[32]		
Units: milligram(s)				
arithmetic mean (standard deviation)				
overall	5.845 (± 3.077)	6.962 (± 3.649)		
week 1	10.959 (± 3.075)	11.722 (± 3.164)		
week 2	8.751 (± 4.009)	9.544 (± 4.545)		
week 3	8.065 (± 4.200)	9.200 (± 4.858)		
week 4	7.411 (± 4.015)	8.567 (± 4.638)		
month 1 to month 3	5.799 (± 3.273)	7.001 (± 3.803)		
month 3 to month 6	4.451 (± 2.871)	5.440 (± 3.232)		

Notes:

[31] - N=200
n overall=200
n w1=200
n w2=194

n w3=193
n w4=191
n month 1 to 3=189
n month 3 to 6=184
[32] - N=201
n overall=201
n w1=201
n w2=197
n w3=195
n w4=193
n month 1 to 3=189
n month 3 to 6=181

Statistical analyses

Statistical analysis title	1_TDD_overall

Statistical analysis description:

For overall TDD (from first dose date to last dose date), the average TDD have been analysed using an ANOVA model.

Comparison groups	1_Envarsus® v 2_Prograf® /Advagraf®
Number of subjects included in analysis	401
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.001 [33]
Method	ANOVA
Parameter estimate	LS Mean difference
Point estimate	-1.109
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.77
upper limit	-0.488

Notes:

[33] - The ANOVA model includes treatment and country as fixed effects.

Statistical analysis title	2_TDD_week1

Statistical analysis description:

average TDD by period have been analysed using a mixed model for repeated measures (MMRM). The MMRM model includes treatment, period, treatment by period interaction and country as fixed effects. An Unstructured covariance structure was used.

Comparison groups	1_Envarsus® v 2_Prograf® /Advagraf®
Number of subjects included in analysis	401
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.013
Method	MMRM
Parameter estimate	LS Mean difference
Point estimate	-0.754
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.347
upper limit	-0.161

Statistical analysis title	3_TDD_week2

Statistical analysis description:

average TDD by period have been analysed using a mixed model for repeated measures (MMRM)
n° of subjects included in this statistical analysis (n) is:
n Envarsus=194 out of 200
n Prograf/Advagraf=197 out of 201
total number = 391 out of 401

Comparison groups	1_Envarsus® v 2_Prograf® /Advagraf®
Number of subjects included in analysis	401
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.064
Method	MMRM
Parameter estimate	LS Mean
Point estimate	-0.788
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.623
upper limit	0.047

Statistical analysis title	4_TDD_week3

Statistical analysis description:

average TDD by period have been analysed using a mixed model for repeated measures (MMRM). The MMRM model includes treatment, period, treatment by period interaction and country as fixed effects. An Unstructured covariance structure was used.
n° of subjects included in this statistical analysis (n) is:
n Envarsus=193 out of 200
n Prograf/Advagraf=195 out of 201
total number = 388 out of 401

Comparison groups	1_Envarsus® v 2_Prograf® /Advagraf®
Number of subjects included in analysis	401
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.018
Method	MMRM
Parameter estimate	LS Mean difference
Point estimate	-1.081
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.976
upper limit	-0.186

Statistical analysis title	5_TDD_week4

Statistical analysis description:

average TDD by period have been analysed using a mixed model for repeated measures (MMRM). The MMRM model includes treatment, period, treatment by period interaction and country as fixed effects. An Unstructured covariance structure was used.
n° of subjects included in this statistical analysis (n) is:
n Envarsus=191 out of 200
n Prograf/Advagraf=193 out of 201
total number = 384 out of 401

Comparison groups	1_Envarsus® v 2_Prograf® /Advagraf®
Number of subjects included in analysis	401
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.008
Method	MMRM
Parameter estimate	LS Mean difference
Point estimate	-1.177
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.049
upper limit	-0.306

Statistical analysis title	6_TDD_month 1 to month 3

Statistical analysis description:

average TDD by period have been analysed using a mixed model for repeated measures (MMRM). The MMRM model includes treatment, period, treatment by period interaction and country as fixed effects. An Unstructured covariance structure was used.
n° of subjects included in this statistical analysis (n) is:
n Envarsus=189 out of 200
n Prograf/Advagraf=189 out of 201
total number = 378 out of 401

Comparison groups	1_Envarsus® v 2_Prograf® /Advagraf®
Number of subjects included in analysis	401
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.001
Method	MMRM
Parameter estimate	LS Mean difference
Point estimate	-1.197
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.91
upper limit	-0.485

Statistical analysis title	7_TDD_month 3 to month 6

Statistical analysis description:

average TDD by period have been analysed using a mixed model for repeated measures (MMRM). The MMRM model includes treatment, period, treatment by period interaction and country as fixed effects.

An Unstructured covariance structure was used.
n° of subjects included in this statistical analysis (n) is:
n Envarsus=184 out of 200
n Prograf/Advagraf=181 out of 201
total number = 365 out of 401

Comparison groups	1_Envarsus® v 2_Prograf® /Advagraf®
Number of subjects included in analysis	401
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.002
Method	MMRM
Parameter estimate	LS Mean difference
Point estimate	-0.984
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.603
upper limit	-0.364

Secondary: 11_Time to Treatment Discontinuation

End point title	11_Time to Treatment Discontinuation

End point description:

Efficacy endpoint.
Time to treatment discontinuation (days) will be calculated as difference between the date of treatment discontinuation for any reason and the date of randomization + 1.
Patients who complete the study will be right-censored at last dose.
Number of subjects censored and event was reported below.
Shown are the number of patients included in the model (modified Intention-to-treat [mITT] population [N]; patients with available results [n])

End point type	Secondary

End point timeframe:

from the randomization day +1

End point values	1_Envarsus®	2_Prograf® /Advagraf®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	200[34]	201[35]		
Units: number of subjects				
subjects censored	177	173		
subjects event	23	28		

Notes:

[34] - N=200;n=200

[35] - N=201;n=201

Statistical analyses

Statistical analysis title	1_Time to treatment discontinuation

Statistical analysis description:

analysis perfomred on censored subjects.

Comparison groups	1_Envarsus® v 2_Prograf® /Advagraf®
Number of subjects included in analysis	401
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.461
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.02

Secondary: 12_Opportunistic Infection

End point title	12_Opportunistic Infection

End point description:

Safety endpoint.
Number of subjects with any opportunistic infection, were presented by treatment group (Envarsus, Prograf/Advagraf) and summarised below.
Shown are the number of patients included in the model (safety population [N]; patients with available results [n])
Any infection that was deemed to have occurred due to the immunosuppression was regarded as an opportunistic infection. In particular, the infections due to the following agents were all considered as opportunistic:
- herpes simplex virus (HSV),
- varicella zoster virus (VZV),
- Epstein-Barr virus (EBV),
-Cytomegalovirus (CMV),
- PcP (Pneumocystitis jiroveci pneumonia)
- Mycobacterium tuberculosis
-Toxoplasma gondii
- Nocardia species
- Listeria monocytogenes infections
- fungi.

End point type	Secondary

End point timeframe:

Overall the study

End point values	1_Envarsus®	2_Prograf® /Advagraf®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	200[36]	201[37]		
Units: number of subject				
subjects	38	40		

Notes:

[36] - N=200;n=200

[37] - N=201;n=201

Statistical analyses

Statistical analysis title	1_opportunistc infection

Statistical analysis description:

A Fisher’s exact test will be used to estimate the difference between treatments.

Comparison groups	1_Envarsus® v 2_Prograf® /Advagraf®
Number of subjects included in analysis	401
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9 [38]
Method	Fisher exact
Parameter estimate	Percentage difference
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.7
upper limit	6.9

Notes:

[38] - P-value was based on a 2-sided Fisher’s exact test to evaluate the difference between treatment groups in the incidence of events. The 95% CI for the difference in proportions between the two treatment groups was based on the Newcombe-Wilson method.

Secondary: 13_BKV Viremia

End point title	13_BKV Viremia

End point description:

Safety endpoint.
The number of subjects with BKV viremia (defined as the presence of BKV viremia detected in the in blood sample by nuclear acid testing),were presented by treatment group (Envarsus, Prograf/Advagraf) and summarised below.
For subjects in the safety analysis set over the entire treatment period.Incidents of BKV viremia was recorded as AEs.
Shown are the number of patients included in the model (safety population [N]; patients with available results [n])

End point type	Secondary

End point timeframe:

Overall treatment period

End point values	1_Envarsus®	2_Prograf® /Advagraf®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	200[39]	201[40]		
Units: number of subject				
total	32	32		
Not clinically significant	24	20		
clinically significant	8	12		

Notes:

[39] - N=200;n=200

[40] - N=201;n=201

Statistical analyses

Statistical analysis title	1_BKV Viremia

Statistical analysis description:

A Fisher’s exact test will be used to estimate the difference between treatments.

Comparison groups	1_Envarsus® v 2_Prograf® /Advagraf®
Number of subjects included in analysis	401
Analysis specification	Pre-specified
Analysis type	other
P-value	> 0.999 [41]
Method	Fisher exact
Parameter estimate	Percentage difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.1
upper limit	7.3

Notes:

[41] - P-value was based on a 2-sided Fisher’s exact test to evaluate the difference between treatment groups in the incidence of events. The 95% CI for the difference in proportions between the two treatment groups was based on the Newcombe-Wilson method.

Secondary: 14_Malignancy

End point title	14_Malignancy

End point description:

Safety endpoint.
The number of subjects with any malignancy was presented by treatment group (Envarsus, Prograf/Advagraf) and summarised below.
Incidents of any malignancy was recorded as AEs.
Shown are the number of patients included in the model (safety population [N]; patients with available results [n])

End point type	Secondary

End point timeframe:

Overall study treatment

End point values	1_Envarsus®	2_Prograf® /Advagraf®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	200[42]	201[43]		
Units: number of subject				
subjects	1	3		

Notes:

[42] - N=200;n=200

[43] - N=201;n=201

Statistical analyses

Statistical analysis title	1_malignancy

Statistical analysis description:

A Fisher’s exact test will be used to estimate the difference between treatments

Comparison groups	1_Envarsus® v 2_Prograf® /Advagraf®
Number of subjects included in analysis	401
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.623 [44]
Method	Fisher exact
Parameter estimate	Percentage difference
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.8
upper limit	1.5

Notes:

[44] - P-value was based on a 2-sided Fisher's exact test to evaluate the difference between treatment groups in the incidence of events. The 95% CI for the difference in proportions between the two treatment
groups was based on the Newcombe-Wilson method.

Secondary: 15_Estimated glomerular filtration rate (eGFR)

End point title	15_Estimated glomerular filtration rate (eGFR)

End point description:

Safety endpoint.
The eGFR was calculated according to the 2009 Chronic Kidney Disease Epidemiology Collaboration creatinine equation, utilising the value of serum creatinine of the day.
For eGFR, baseline was defined as the Visit 10 (Study Day 28) evaluation. Change from baseline for eGFR results have been reported from day 60 to day 180.
Shown are the number of patients included in the model (safety population [N]; patients with available results [n])

End point type	Secondary

End point timeframe:

untill month 6

End point values	1_Envarsus®	2_Prograf® /Advagraf®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	200[45]	201[46]		
Units: ml/min per 1.73m2				
arithmetic mean (standard deviation)				
change from baseline_day 60	1.846 (± 10.837)	0.877 (± 10.382)		
change from baseline_day 90	1.214 (± 12.564)	1.830 (± 12.038)		
change from baseline_day 120	2.566 (± 13.348)	2.797 (± 12.997)		
change from baseline_day 150	2.083 (± 14.434)	4.073 (± 13.342)		
change from baseline_day 180	3.196 (± 13.247)	4.654 (± 14.132)		

Notes:

[45] - N=200
n day 60 =184
n day 90 =180
n day 120 =178
n day 150 =176

n day 180 =175

[46] - N=201
n day 60 =185
n day 90 =180
n day 120 =178
n day 150 =175
n day 180 =171

Statistical analyses

Statistical analysis title	1_eGFR_day 60

Statistical analysis description:

A mixed model for repeated measures (MMRM) will be performed.The MMRM model includes treatment, visit, treatment by visit interaction and country as fixed effects, and baseline
eGFR value at Day 28 (Visit 10) as covariate. An Unstructured covariance structure was used.
n° of subjects included in this statistical analysis (n) is:
n Envarsus=184 out of 200
n Prograf/Advagraf=185 out of 201
total number = 369 out of 401

Comparison groups	1_Envarsus® v 2_Prograf® /Advagraf®
Number of subjects included in analysis	401
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.285
Method	MMRM
Parameter estimate	LS Mean difference
Point estimate	1.146
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.958
upper limit	3.25

Statistical analysis title	2_eGFR_day 90

Statistical analysis description:

A mixed model for repeated measures (MMRM) will be performed.The MMRM model includes treatment, visit, treatment by visit interaction and country as fixed effects, and baseline
eGFR value at Day 28 (Visit 10) as covariate. An Unstructured covariance structure was used.
n° of subjects included in this statistical analysis (n) is:
n Envarsus=180 out of 200
n Prograf/Advagraf=180 out of 201
total number = 360 out of 401

Comparison groups	1_Envarsus® v 2_Prograf® /Advagraf®
Number of subjects included in analysis	401
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.59
Method	MMRM
Parameter estimate	LS Mean difference
Point estimate	-0.649

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.013
upper limit	1.716

Statistical analysis title	3_eGFR_day 120

Statistical analysis description:

A mixed model for repeated measures (MMRM) will be performed.The MMRM model includes treatment, visit, treatment by visit interaction and country as fixed effects, and baseline
eGFR value at Day 28 (Visit 10) as covariate. An Unstructured covariance structure was used.
n° of subjects included in this statistical analysis (n) is:
n Envarsus=178 out of 200
n Prograf/Advagraf=178 out of 201
total number = 356 out of 401

Comparison groups	1_Envarsus® v 2_Prograf® /Advagraf®
Number of subjects included in analysis	401
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.783
Method	MMRM
Parameter estimate	LS Mean difference
Point estimate	-0.346
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.821
upper limit	2.129

Statistical analysis title	4_eGFR_day 150

Statistical analysis description:

A mixed model for repeated measures (MMRM) will be performed.The MMRM model includes treatment, visit, treatment by visit interaction and country as fixed effects, and baseline eGFR value at Day 28 (Visit 10) as covariate. An Unstructured covariance structure was used.
n° of subjects included in this statistical analysis (n) is:
n Envarsus=176 out of 200
n Prograf/Advagraf=175 out of 201
total number = 351 out of 401

Comparison groups	1_Envarsus® v 2_Prograf® /Advagraf®
Number of subjects included in analysis	401
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.323
Method	MMRM
Parameter estimate	LS Mean difference
Point estimate	-1.383

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.13
upper limit	1.364

Statistical analysis title	5_eGFR_day 180

Statistical analysis description:

A mixed model for repeated measures (MMRM) will be performed.The MMRM model includes treatment, visit, treatment by visit interaction and country as fixed effects, and baseline
eGFR value at Day 28 (Visit 10) as covariate. An Unstructured covariance structure was used.
n° of subjects included in this statistical analysis (n) is:
n Envarsus=175 out of 200
n Prograf/Advagraf=171 out of 201
total number = 346 out of 401

Comparison groups	1_Envarsus® v 2_Prograf® /Advagraf®
Number of subjects included in analysis	401
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.426
Method	MMRM
Parameter estimate	LS Mean difference
Point estimate	-1.093
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.79
upper limit	1.604

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From day -28 to day 180+/-7	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups	
Reporting group title	1_Envarsus®

Reporting group description:

Active Treatment Arm with Envarsus tablets: randomization 1:1 ratio (Arm1: Arm2). Active substance: Tacrolimus monohydrate.
Oral administration once daily.
starting dose: 0.17mg/kg/day
Whatever the treatment, patients will have their dose adjusted to maintain tacrolimus whole blood trough levels within the standard reference ranges of 5-15 ng/ml in the first three months after transplantation and 5-10 ng/ml afterwards.

Reporting group title	2_Prograf® /Advagraf®

Reporting group description:

Reference therapy arm (Arm2) with randomization 1:1 ratio (Arm1: Arm2) (active substance: Tacrolimus monohydrate)
- Prograf® capsules will be administered orally. The treatment should commence at the starting total daily dose of 0.2 mg/kg/day delivered in two equally divided doses 12 hours apart (one in the morning and one in the evening) or
- Advagraf® capsules will be administered orally. The treatment should commence at the starting total daily dose of 0.2 mg/kg/day administered once daily in the morning.
Whatever the treatment, patients will have their dose adjusted to maintain tacrolimus whole blood trough levels within the standard reference ranges of 5-15 ng/ml in the first three months after transplantation and 5-10 ng/ml afterwards.

Serious adverse events	1_Envarsus®	2_Prograf® /Advagraf®	
Total subjects affected by serious adverse events			
subjects affected / exposed	99 / 200 (49.50%)	93 / 201 (46.27%)	
number of deaths (all causes)	4	4	
number of deaths resulting from adverse events	1	0	
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial haemorrhage			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood pressure fluctuation			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	2 / 200 (1.00%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal haematoma			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphocele			
subjects affected / exposed	4 / 200 (2.00%)	4 / 201 (1.99%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic venous thrombosis			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyarteritis nodosa			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	2 / 200 (1.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

Chest pain			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
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	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device pain			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	1 / 200 (0.50%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Oedema peripheral			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multimorbidity			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Immune system disorders			

Transplant rejection			
subjects affected / exposed	9 / 200 (4.50%)	8 / 201 (3.98%)	
occurrences causally related to treatment / all	2 / 9	2 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Prostatic obstruction			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	0 / 200 (0.00%)	4 / 201 (1.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bronchitis chronic			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 200 (0.50%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 200 (0.50%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			

subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	10 / 200 (5.00%)	2 / 201 (1.00%)	
occurrences causally related to treatment / all	4 / 10	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Anastomotic stenosis			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (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	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder injury			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complications of transplanted kidney			
subjects affected / exposed	12 / 200 (6.00%)	2 / 201 (1.00%)	
occurrences causally related to treatment / all	3 / 13	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fascial rupture			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (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	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incision site haematoma			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perirenal haematoma			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural urine leak			
subjects affected / exposed	2 / 200 (1.00%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal haematoma			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal transplant failure			

subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (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	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transplant dysfunction			
subjects affected / exposed	0 / 200 (0.00%)	2 / 201 (1.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transplant failure			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention postoperative			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular graft thrombosis			
subjects affected / exposed	2 / 200 (1.00%)	4 / 201 (1.99%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	1 / 200 (0.50%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound haematoma			

subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 200 (0.50%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 200 (0.00%)	2 / 201 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	3 / 200 (1.50%)	3 / 201 (1.49%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure			
subjects affected / exposed	0 / 200 (0.00%)	2 / 201 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 200 (0.50%)	3 / 201 (1.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Stress cardiomyopathy			

subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (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	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised tonic-clonic seizure			
subjects affected / exposed	1 / 200 (0.50%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic encephalopathy			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (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			

Febrile bone marrow aplasia			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	2 / 200 (1.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic microangiopathy			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
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	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	3 / 200 (1.50%)	7 / 201 (3.48%)	
occurrences causally related to treatment / all	0 / 3	2 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			

subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastric ulcer			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Large intestinal haemorrhage			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal ulcer			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis ulcerative			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			

subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Subileus			
subjects affected / exposed	1 / 200 (0.50%)	2 / 201 (1.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Anuria			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysuria			
subjects affected / exposed	3 / 200 (1.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glomerulonephritis proliferative			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	1 / 200 (0.50%)	3 / 201 (1.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrectasia			

subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephropathy toxic			
subjects affected / exposed	2 / 200 (1.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
obstructive uropathy			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postrenal failure			
subjects affected / exposed	3 / 200 (1.50%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal aneurysm			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal artery stenosis			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	3 / 200 (1.50%)	2 / 201 (1.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	1 / 200 (0.50%)	4 / 201 (1.99%)	
occurrences causally related to treatment / all	1 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal necrosis			

subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal tubular necrosis			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteral disorder			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteral necrosis			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric dilatation			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric stenosis			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral disorder			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary fistula			
subjects affected / exposed	2 / 200 (1.00%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			

subjects affected / exposed	2 / 200 (1.00%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vesical fistula			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (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	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle haemorrhage			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Anal abscess			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bacterial infection			
subjects affected / exposed	2 / 200 (1.00%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial pyelonephritis			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter infection			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Citrobacter infection			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis escherichia			
subjects affected / exposed	1 / 200 (0.50%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis klebsiella			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus gastroenteritis			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			

subjects affected / exposed	5 / 200 (2.50%)	2 / 201 (1.00%)	
occurrences causally related to treatment / all	2 / 6	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
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	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia infection			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia pyelonephritis			
subjects affected / exposed	1 / 200 (0.50%)	2 / 201 (1.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	3 / 200 (1.50%)	4 / 201 (1.99%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis clostridial			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis norovirus			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			

subjects affected / exposed	2 / 200 (1.00%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	2 / 200 (1.00%)	4 / 201 (1.99%)	
occurrences causally related to treatment / all	0 / 2	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella bacteraemia			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella sepsis			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mycotic aneurysm			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nosocomial infection			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral candidiasis			

subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 200 (0.00%)	2 / 201 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 200 (0.00%)	3 / 201 (1.49%)	
occurrences causally related to treatment / all	0 / 0	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyomavirus-associated nephropathy			
subjects affected / exposed	1 / 200 (0.50%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural infection			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonas infection			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonal sepsis			

subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	5 / 200 (2.50%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	2 / 7	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	2 / 200 (1.00%)	5 / 201 (2.49%)	
occurrences causally related to treatment / all	1 / 2	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 200 (0.00%)	2 / 201 (1.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	3 / 200 (1.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	1 / 6	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Streptococcal bacteraemia			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transplant abscess			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			
subjects affected / exposed	2 / 200 (1.00%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	6 / 200 (3.00%)	11 / 201 (5.47%)	
occurrences causally related to treatment / all	1 / 7	5 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	5 / 200 (2.50%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	2 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicella			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection bacterial			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection fungal			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	2 / 200 (1.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			

subjects affected / exposed	2 / 200 (1.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
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	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	1_Envarsus®	2_Prograf® /Advagraf®	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	187 / 200 (93.50%)	188 / 201 (93.53%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Mycosis fungoides			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Prostatic adenoma			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Renal cancer			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Skin cancer			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	

Vulvovaginal warts			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Arterial disorder			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Arteriovenous fistula			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Deep vein thrombosis			
subjects affected / exposed	2 / 200 (1.00%)	3 / 201 (1.49%)	
occurrences (all)	2	3	
Haematoma			
subjects affected / exposed	3 / 200 (1.50%)	2 / 201 (1.00%)	
occurrences (all)	3	2	
Hot flush			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Hypertension			
subjects affected / exposed	39 / 200 (19.50%)	29 / 201 (14.43%)	
occurrences (all)	41	30	
Hypertensive crisis			
subjects affected / exposed	2 / 200 (1.00%)	2 / 201 (1.00%)	
occurrences (all)	2	3	
Hypotension			
subjects affected / exposed	8 / 200 (4.00%)	6 / 201 (2.99%)	
occurrences (all)	8	6	
Intra-abdominal haematoma			
subjects affected / exposed	3 / 200 (1.50%)	0 / 201 (0.00%)	
occurrences (all)	3	0	
Jugular vein thrombosis			

subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Lymphocele			
subjects affected / exposed	4 / 200 (2.00%)	9 / 201 (4.48%)	
occurrences (all)	4	9	
Lymphorrhoea			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Orthostatic hypotension			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Peripheral artery stenosis			
subjects affected / exposed	0 / 200 (0.00%)	4 / 201 (1.99%)	
occurrences (all)	0	4	
Phlebitis			
subjects affected / exposed	1 / 200 (0.50%)	1 / 201 (0.50%)	
occurrences (all)	1	1	
Secondary hypertension			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Thrombophlebitis			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Thrombosis			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	2	
Vascular pain			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
Acute phase reaction			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Administration site inflammation			

subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Asthenia			
subjects affected / exposed	6 / 200 (3.00%)	6 / 201 (2.99%)	
occurrences (all)	6	7	
Catheter site inflammation			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Catheter site pain			
subjects affected / exposed	1 / 200 (0.50%)	6 / 201 (2.99%)	
occurrences (all)	1	6	
Chest discomfort			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Chest pain			
subjects affected / exposed	2 / 200 (1.00%)	2 / 201 (1.00%)	
occurrences (all)	2	2	
Chills			
subjects affected / exposed	1 / 200 (0.50%)	2 / 201 (1.00%)	
occurrences (all)	1	2	
Decreased activity			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Device dislocation			
subjects affected / exposed	0 / 200 (0.00%)	2 / 201 (1.00%)	
occurrences (all)	0	2	
Face oedema			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	6 / 200 (3.00%)	8 / 201 (3.98%)	
occurrences (all)	6	8	
Feeling hot			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Fibrosis			

subjects affected / exposed	2 / 200 (1.00%)	2 / 201 (1.00%)	
occurrences (all)	2	2	
Impaired healing			
subjects affected / exposed	2 / 200 (1.00%)	2 / 201 (1.00%)	
occurrences (all)	2	2	
Implant site extravasation			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Influenza like illness			
subjects affected / exposed	3 / 200 (1.50%)	1 / 201 (0.50%)	
occurrences (all)	3	1	
Localised oedema			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Malaise			
subjects affected / exposed	3 / 200 (1.50%)	1 / 201 (0.50%)	
occurrences (all)	4	1	
Medical device complication			
subjects affected / exposed	1 / 200 (0.50%)	3 / 201 (1.49%)	
occurrences (all)	1	3	
Medical device pain			
subjects affected / exposed	4 / 200 (2.00%)	1 / 201 (0.50%)	
occurrences (all)	5	1	
Non-cardiac chest pain			
subjects affected / exposed	5 / 200 (2.50%)	0 / 201 (0.00%)	
occurrences (all)	5	0	
Oedema peripheral			
subjects affected / exposed	36 / 200 (18.00%)	30 / 201 (14.93%)	
occurrences (all)	43	30	
Oedema			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Pain			
subjects affected / exposed	3 / 200 (1.50%)	4 / 201 (1.99%)	
occurrences (all)	3	4	
Pyrexia			

subjects affected / exposed	21 / 200 (10.50%)	9 / 201 (4.48%)	
occurrences (all)	23	11	
Xerosis			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Hypogammaglobulinaemia			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Seasonal allergy			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Transplant rejection			
subjects affected / exposed	9 / 200 (4.50%)	4 / 201 (1.99%)	
occurrences (all)	10	4	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 200 (0.50%)	6 / 201 (2.99%)	
occurrences (all)	1	6	
Breast mass			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Dysmenorrhoea			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Erectile dysfunction			
subjects affected / exposed	1 / 200 (0.50%)	1 / 201 (0.50%)	
occurrences (all)	1	1	
Gynaecomastia			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Ovarian cyst			

subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Pelvic haematoma			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Penile oedema			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Penile pain			
subjects affected / exposed	1 / 200 (0.50%)	2 / 201 (1.00%)	
occurrences (all)	1	3	
Prostatomegaly			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Rectocele			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Scrotal oedema			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Scrotal swelling			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Testicular oedema			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Testicular pain			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Testicular swelling			
subjects affected / exposed	1 / 200 (0.50%)	2 / 201 (1.00%)	
occurrences (all)	1	2	
Vulvovaginal pruritus			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal			

disorders				
Acute pulmonary oedema				
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)		
occurrences (all)	1	0		
Atelectasis				
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)		
occurrences (all)	1	0		
Bronchial irritation				
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)		
occurrences (all)	0	1		
Chronic obstructive pulmonary disease				
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)		
occurrences (all)	1	0		
Cough				
subjects affected / exposed	11 / 200 (5.50%)	9 / 201 (4.48%)		
occurrences (all)	11	10		
Dyspnoea				
subjects affected / exposed	11 / 200 (5.50%)	9 / 201 (4.48%)		
occurrences (all)	11	9		
Hiccups				
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)		
occurrences (all)	1	0		
Nasal congestion				
subjects affected / exposed	2 / 200 (1.00%)	1 / 201 (0.50%)		
occurrences (all)	2	1		
Oropharyngeal pain				
subjects affected / exposed	2 / 200 (1.00%)	2 / 201 (1.00%)		
occurrences (all)	2	3		
Pleural effusion				
subjects affected / exposed	1 / 200 (0.50%)	2 / 201 (1.00%)		
occurrences (all)	1	2		
Pneumothorax				
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)		
occurrences (all)	1	0		
Productive cough				

subjects affected / exposed	3 / 200 (1.50%)	2 / 201 (1.00%)	
occurrences (all)	3	2	
Pulmonary venous thrombosis			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Rales			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Respiratory failure			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Rhinorrhoea			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Sinus congestion			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Sputum increased			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Throat irritation			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Wheezing			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 200 (0.50%)	4 / 201 (1.99%)	
occurrences (all)	1	4	
Anxiety disorder			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Anxiety			
subjects affected / exposed	13 / 200 (6.50%)	9 / 201 (4.48%)	
occurrences (all)	13	10	

Confusional state			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Depression			
subjects affected / exposed	1 / 200 (0.50%)	3 / 201 (1.49%)	
occurrences (all)	1	3	
Dysthymic disorder			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Emotional distress			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Hallucination			
subjects affected / exposed	1 / 200 (0.50%)	1 / 201 (0.50%)	
occurrences (all)	1	1	
Insomnia			
subjects affected / exposed	21 / 200 (10.50%)	20 / 201 (9.95%)	
occurrences (all)	21	22	
Mental disorder			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Nervousness			
subjects affected / exposed	1 / 200 (0.50%)	1 / 201 (0.50%)	
occurrences (all)	1	1	
Restlessness			
subjects affected / exposed	1 / 200 (0.50%)	2 / 201 (1.00%)	
occurrences (all)	1	2	
Sleep disorder			
subjects affected / exposed	5 / 200 (2.50%)	8 / 201 (3.98%)	
occurrences (all)	6	8	
Investigations			
Acid base balance abnormal			
subjects affected / exposed	2 / 200 (1.00%)	0 / 201 (0.00%)	
occurrences (all)	2	0	
Alanine aminotransferase increased			

subjects affected / exposed	2 / 200 (1.00%)	2 / 201 (1.00%)	
occurrences (all)	2	2	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Blood bicarbonate decreased			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Blood calcium decreased			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Blood cholesterol increased			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Blood creatinine increased			
subjects affected / exposed	6 / 200 (3.00%)	5 / 201 (2.49%)	
occurrences (all)	6	5	
Blood glucose abnormal			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Blood glucose increased			
subjects affected / exposed	1 / 200 (0.50%)	1 / 201 (0.50%)	
occurrences (all)	1	1	
Blood lactate dehydrogenase increased			
subjects affected / exposed	2 / 200 (1.00%)	3 / 201 (1.49%)	
occurrences (all)	2	3	
Blood phosphorus decreased			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Blood potassium increased			

subjects affected / exposed	1 / 200 (0.50%)	1 / 201 (0.50%)	
occurrences (all)	1	1	
Blood pressure increased			
subjects affected / exposed	0 / 200 (0.00%)	3 / 201 (1.49%)	
occurrences (all)	0	3	
Blood pressure systolic increased			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Blood sodium decreased			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Blood sodium increased			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
C-reactive protein increased			
subjects affected / exposed	2 / 200 (1.00%)	0 / 201 (0.00%)	
occurrences (all)	2	0	
Cardiac murmur			
subjects affected / exposed	1 / 200 (0.50%)	1 / 201 (0.50%)	
occurrences (all)	1	1	
Coagulation factor			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Cytomegalovirus test positive			
subjects affected / exposed	3 / 200 (1.50%)	4 / 201 (1.99%)	
occurrences (all)	3	4	
Electrocardiogram abnormal			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	2	0	
Enterococcus test positive			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Escherichia test positive			
subjects affected / exposed	1 / 200 (0.50%)	1 / 201 (0.50%)	
occurrences (all)	1	1	
Fungal test positive			

subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)		
occurrences (all)	1	0		
Glucose tolerance test abnormal				
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)		
occurrences (all)	0	1		
Glycosylated haemoglobin increased				
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)		
occurrences (all)	1	0		
Haematocrit decreased				
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)		
occurrences (all)	0	1		
Haemoglobin decreased				
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)		
occurrences (all)	1	0		
Hepatic enzyme increased				
subjects affected / exposed	1 / 200 (0.50%)	1 / 201 (0.50%)		
occurrences (all)	1	1		
Immunosuppressant drug level increased				
subjects affected / exposed	1 / 200 (0.50%)	2 / 201 (1.00%)		
occurrences (all)	1	2		
Inflammatory marker increased				
subjects affected / exposed	2 / 200 (1.00%)	0 / 201 (0.00%)		
occurrences (all)	2	0		
Liver function test abnormal				
subjects affected / exposed	1 / 200 (0.50%)	2 / 201 (1.00%)		
occurrences (all)	2	2		
Low density lipoprotein increased				
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)		
occurrences (all)	1	0		
Oxygen saturation decreased				
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)		
occurrences (all)	1	0		
Polyomavirus test positive				
subjects affected / exposed	4 / 200 (2.00%)	1 / 201 (0.50%)		
occurrences (all)	4	1		

Red blood cell count decreased			
subjects affected / exposed	0 / 200 (0.00%)	2 / 201 (1.00%)	
occurrences (all)	0	2	
Renal function test abnormal			
subjects affected / exposed	1 / 200 (0.50%)	1 / 201 (0.50%)	
occurrences (all)	1	1	
Staphylococcus test positive			
subjects affected / exposed	0 / 200 (0.00%)	2 / 201 (1.00%)	
occurrences (all)	0	2	
Transaminases increased			
subjects affected / exposed	2 / 200 (1.00%)	2 / 201 (1.00%)	
occurrences (all)	2	2	
Viral test positive			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Volume blood decreased			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Weight decreased			
subjects affected / exposed	0 / 200 (0.00%)	2 / 201 (1.00%)	
occurrences (all)	0	2	
Weight increased			
subjects affected / exposed	3 / 200 (1.50%)	3 / 201 (1.49%)	
occurrences (all)	3	3	
White blood cell count decreased			
subjects affected / exposed	0 / 200 (0.00%)	3 / 201 (1.49%)	
occurrences (all)	0	3	
Injury, poisoning and procedural complications			
Anaemia postoperative			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Anaesthetic complication			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Arteriovenous fistula site complication			

subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Arteriovenous fistula thrombosis			
subjects affected / exposed	3 / 200 (1.50%)	3 / 201 (1.49%)	
occurrences (all)	3	3	
Chronic allograft nephropathy			
subjects affected / exposed	1 / 200 (0.50%)	3 / 201 (1.49%)	
occurrences (all)	1	3	
Complications of transplant surgery			
subjects affected / exposed	1 / 200 (0.50%)	2 / 201 (1.00%)	
occurrences (all)	1	2	
Complications of transplanted kidney			
subjects affected / exposed	22 / 200 (11.00%)	28 / 201 (13.93%)	
occurrences (all)	25	28	
Contusion			
subjects affected / exposed	2 / 200 (1.00%)	0 / 201 (0.00%)	
occurrences (all)	2	0	
Face injury			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Fall			
subjects affected / exposed	2 / 200 (1.00%)	1 / 201 (0.50%)	
occurrences (all)	2	1	
Foot fracture			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Graft complication			
subjects affected / exposed	4 / 200 (2.00%)	0 / 201 (0.00%)	
occurrences (all)	4	0	
Incisional hernia			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Laceration			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Overdose			

subjects affected / exposed	0 / 200 (0.00%)	2 / 201 (1.00%)	
occurrences (all)	0	2	
Perirenal haematoma			
subjects affected / exposed	0 / 200 (0.00%)	2 / 201 (1.00%)	
occurrences (all)	0	2	
Post procedural complication			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Post procedural haematoma			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Postoperative wound complication			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Procedural anxiety			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Procedural pain			
subjects affected / exposed	7 / 200 (3.50%)	6 / 201 (2.99%)	
occurrences (all)	7	6	
Radius fracture			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Renal haematoma			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Rib fracture			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Scrotal haematoma			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Seroma			
subjects affected / exposed	3 / 200 (1.50%)	0 / 201 (0.00%)	
occurrences (all)	3	0	
Shunt thrombosis			

subjects affected / exposed	0 / 200 (0.00%)	2 / 201 (1.00%)	
occurrences (all)	0	2	
Subcutaneous haematoma			
subjects affected / exposed	2 / 200 (1.00%)	0 / 201 (0.00%)	
occurrences (all)	2	0	
Toxicity to various agents			
subjects affected / exposed	2 / 200 (1.00%)	2 / 201 (1.00%)	
occurrences (all)	2	2	
Transplant dysfunction			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Transplantation complication			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Wound complication			
subjects affected / exposed	9 / 200 (4.50%)	17 / 201 (8.46%)	
occurrences (all)	10	17	
Wound dehiscence			
subjects affected / exposed	1 / 200 (0.50%)	1 / 201 (0.50%)	
occurrences (all)	1	1	
Wound haematoma			
subjects affected / exposed	0 / 200 (0.00%)	2 / 201 (1.00%)	
occurrences (all)	0	2	
Congenital, familial and genetic disorders			
Hydrocele			
subjects affected / exposed	2 / 200 (1.00%)	2 / 201 (1.00%)	
occurrences (all)	2	2	
Hypertrophic cardiomyopathy			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	3 / 200 (1.50%)	4 / 201 (1.99%)	
occurrences (all)	3	4	
Atrial fibrillation			

subjects affected / exposed	2 / 200 (1.00%)	5 / 201 (2.49%)	
occurrences (all)	2	6	
Bradycardia			
subjects affected / exposed	1 / 200 (0.50%)	1 / 201 (0.50%)	
occurrences (all)	1	1	
Cardiac arrest			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Extrasystoles			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Mitral valve incompetence			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Palpitations			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Sinus bradycardia			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Sinus tachycardia			
subjects affected / exposed	1 / 200 (0.50%)	6 / 201 (2.99%)	
occurrences (all)	1	6	
Tachyarrhythmia			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Tachycardia			
subjects affected / exposed	5 / 200 (2.50%)	3 / 201 (1.49%)	
occurrences (all)	5	3	
Ventricular extrasystoles			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Nervous system disorders			
Balance disorder			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	

Brachial plexopathy			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Carotid arteriosclerosis			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Cerebral infarction			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Dizziness			
subjects affected / exposed	2 / 200 (1.00%)	2 / 201 (1.00%)	
occurrences (all)	2	2	
Dysaesthesia			
subjects affected / exposed	3 / 200 (1.50%)	0 / 201 (0.00%)	
occurrences (all)	3	0	
Dysgeusia			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Dyskinesia			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	18 / 200 (9.00%)	12 / 201 (5.97%)	
occurrences (all)	19	13	
Meralgia paraesthetica			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Monoparesis			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Neuralgia			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Paraesthesia			
subjects affected / exposed	3 / 200 (1.50%)	1 / 201 (0.50%)	
occurrences (all)	3	1	

Presyncope			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Resting tremor			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Restless legs syndrome			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Sciatica			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Somnolence			
subjects affected / exposed	0 / 200 (0.00%)	2 / 201 (1.00%)	
occurrences (all)	0	2	
Syncope			
subjects affected / exposed	1 / 200 (0.50%)	1 / 201 (0.50%)	
occurrences (all)	1	1	
Tremor			
subjects affected / exposed	37 / 200 (18.50%)	23 / 201 (11.44%)	
occurrences (all)	39	24	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	67 / 200 (33.50%)	66 / 201 (32.84%)	
occurrences (all)	68	68	
Bone marrow failure			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Coagulopathy			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Febrile neutropenia			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Leukocytosis			

subjects affected / exposed	15 / 200 (7.50%)	9 / 201 (4.48%)	
occurrences (all)	17	9	
Leukopenia			
subjects affected / exposed	25 / 200 (12.50%)	28 / 201 (13.93%)	
occurrences (all)	26	30	
Lymph node pain			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Lymphadenopathy			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Lymphopenia			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Nephrogenic anaemia			
subjects affected / exposed	6 / 200 (3.00%)	5 / 201 (2.49%)	
occurrences (all)	7	5	
Neutropenia			
subjects affected / exposed	7 / 200 (3.50%)	5 / 201 (2.49%)	
occurrences (all)	7	5	
Neutrophilia			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Pancytopenia			
subjects affected / exposed	3 / 200 (1.50%)	0 / 201 (0.00%)	
occurrences (all)	3	0	
Polycythaemia			
subjects affected / exposed	1 / 200 (0.50%)	2 / 201 (1.00%)	
occurrences (all)	1	2	
Splenomegaly			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Thrombocytopenia			
subjects affected / exposed	8 / 200 (4.00%)	3 / 201 (1.49%)	
occurrences (all)	9	3	
Thrombocytosis			

subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Hypoacusis			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Tinnitus			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Vertigo			
subjects affected / exposed	1 / 200 (0.50%)	1 / 201 (0.50%)	
occurrences (all)	1	1	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	2	0	
Chorioretinopathy			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Conjunctival haemorrhage			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Corneal erosion			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Dry eye			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Retinal vascular thrombosis			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Uveitis			

subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Vision blurred			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Visual impairment			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Vitreous detachment			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	2 / 200 (1.00%)	0 / 201 (0.00%)	
occurrences (all)	2	0	
Abdominal distension			
subjects affected / exposed	3 / 200 (1.50%)	2 / 201 (1.00%)	
occurrences (all)	3	2	
Abdominal hernia			
subjects affected / exposed	0 / 200 (0.00%)	2 / 201 (1.00%)	
occurrences (all)	0	2	
Abdominal pain upper			
subjects affected / exposed	5 / 200 (2.50%)	1 / 201 (0.50%)	
occurrences (all)	5	1	
Abdominal pain			
subjects affected / exposed	19 / 200 (9.50%)	21 / 201 (10.45%)	
occurrences (all)	20	21	
Abdominal wall haematoma			
subjects affected / exposed	2 / 200 (1.00%)	0 / 201 (0.00%)	
occurrences (all)	2	0	
Abnormal faeces			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Anal fissure			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	

Anorectal discomfort			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Aphthous stomatitis			
subjects affected / exposed	0 / 200 (0.00%)	2 / 201 (1.00%)	
occurrences (all)	0	2	
Cheilitis			
subjects affected / exposed	1 / 200 (0.50%)	1 / 201 (0.50%)	
occurrences (all)	1	1	
Colitis			
subjects affected / exposed	1 / 200 (0.50%)	1 / 201 (0.50%)	
occurrences (all)	1	1	
Constipation			
subjects affected / exposed	24 / 200 (12.00%)	35 / 201 (17.41%)	
occurrences (all)	25	36	
Diarrhoea			
subjects affected / exposed	40 / 200 (20.00%)	36 / 201 (17.91%)	
occurrences (all)	50	41	
Dry mouth			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Dysbacteriosis			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Dyspepsia			
subjects affected / exposed	6 / 200 (3.00%)	12 / 201 (5.97%)	
occurrences (all)	6	12	
Dysphagia			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Flatulence			
subjects affected / exposed	2 / 200 (1.00%)	1 / 201 (0.50%)	
occurrences (all)	2	1	
Functional gastrointestinal disorder			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	

Gastric dilatation				
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)		
occurrences (all)	0	1		
Gastric ulcer				
subjects affected / exposed	2 / 200 (1.00%)	0 / 201 (0.00%)		
occurrences (all)	2	0		
Gastritis erosive				
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)		
occurrences (all)	0	1		
Gastritis				
subjects affected / exposed	1 / 200 (0.50%)	2 / 201 (1.00%)		
occurrences (all)	1	2		
Gastrointestinal motility disorder				
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)		
occurrences (all)	1	0		
Gastrointestinal pain				
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)		
occurrences (all)	0	1		
Gastrooesophageal reflux disease				
subjects affected / exposed	3 / 200 (1.50%)	4 / 201 (1.99%)		
occurrences (all)	3	4		
Gingival hyperplasia				
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)		
occurrences (all)	1	0		
Gingival inflammation				
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)		
occurrences (all)	1	0		
Gingival swelling				
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)		
occurrences (all)	1	0		
Haematemesis				
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)		
occurrences (all)	1	0		
Haemorrhoids				
subjects affected / exposed	6 / 200 (3.00%)	6 / 201 (2.99%)		
occurrences (all)	6	6		

Ileus paralytic			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Ileus			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Inguinal hernia			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Intestinal obstruction			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Lip dry			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Melaena			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	21 / 200 (10.50%)	16 / 201 (7.96%)	
occurrences (all)	22	18	
Oral mucosa erosion			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Oral pain			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Pancreatitis chronic			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Reactive gastropathy			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Rectal haemorrhage			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	

Stomatitis			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Varices oesophageal			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	13 / 200 (6.50%)	12 / 201 (5.97%)	
occurrences (all)	14	13	
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	4 / 200 (2.00%)	1 / 201 (0.50%)	
occurrences (all)	4	1	
Drug-induced liver injury			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Hepatic function abnormal			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Hepatitis			
subjects affected / exposed	2 / 200 (1.00%)	0 / 201 (0.00%)	
occurrences (all)	2	0	
Hepatocellular injury			
subjects affected / exposed	1 / 200 (0.50%)	1 / 201 (0.50%)	
occurrences (all)	1	1	
Hypertransaminasaemia			
subjects affected / exposed	1 / 200 (0.50%)	1 / 201 (0.50%)	
occurrences (all)	1	1	
Jaundice cholestatic			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Liver disorder			
subjects affected / exposed	1 / 200 (0.50%)	1 / 201 (0.50%)	
occurrences (all)	1	1	
Skin and subcutaneous tissue disorders			

Acne			
subjects affected / exposed	3 / 200 (1.50%)	0 / 201 (0.00%)	
occurrences (all)	3	0	
Alopecia			
subjects affected / exposed	4 / 200 (2.00%)	5 / 201 (2.49%)	
occurrences (all)	4	5	
Capillaritis			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Dermatitis acneiform			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Dermatitis			
subjects affected / exposed	1 / 200 (0.50%)	1 / 201 (0.50%)	
occurrences (all)	1	1	
Diabetic foot			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Dry skin			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Ecchymosis			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Eczema			
subjects affected / exposed	1 / 200 (0.50%)	1 / 201 (0.50%)	
occurrences (all)	1	1	
Erythema			
subjects affected / exposed	2 / 200 (1.00%)	1 / 201 (0.50%)	
occurrences (all)	2	1	
Night sweats			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Petechiae			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	

Pityriasis			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Prurigo			
subjects affected / exposed	2 / 200 (1.00%)	0 / 201 (0.00%)	
occurrences (all)	3	0	
Pruritus allergic			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Pruritus generalised			
subjects affected / exposed	2 / 200 (1.00%)	2 / 201 (1.00%)	
occurrences (all)	2	2	
Pruritus			
subjects affected / exposed	4 / 200 (2.00%)	0 / 201 (0.00%)	
occurrences (all)	4	0	
Rash pruritic			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	5 / 200 (2.50%)	0 / 201 (0.00%)	
occurrences (all)	5	0	
Scar pain			
subjects affected / exposed	1 / 200 (0.50%)	1 / 201 (0.50%)	
occurrences (all)	1	1	
Skin lesion			
subjects affected / exposed	1 / 200 (0.50%)	1 / 201 (0.50%)	
occurrences (all)	1	1	
Skin ulcer			
subjects affected / exposed	1 / 200 (0.50%)	1 / 201 (0.50%)	
occurrences (all)	1	1	
Urticaria			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Albuminuria			

subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Anuria			
subjects affected / exposed	2 / 200 (1.00%)	1 / 201 (0.50%)	
occurrences (all)	2	1	
Azotaemia			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Bladder pain			
subjects affected / exposed	1 / 200 (0.50%)	4 / 201 (1.99%)	
occurrences (all)	1	4	
Bladder spasm			
subjects affected / exposed	11 / 200 (5.50%)	8 / 201 (3.98%)	
occurrences (all)	12	8	
Dysuria			
subjects affected / exposed	7 / 200 (3.50%)	3 / 201 (1.49%)	
occurrences (all)	8	3	
Haematuria			
subjects affected / exposed	14 / 200 (7.00%)	10 / 201 (4.98%)	
occurrences (all)	15	10	
Haemorrhage urinary tract			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Hydronephrosis			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	2	0	
Hypertonic bladder			
subjects affected / exposed	1 / 200 (0.50%)	2 / 201 (1.00%)	
occurrences (all)	1	2	
Leukocyturia			
subjects affected / exposed	4 / 200 (2.00%)	2 / 201 (1.00%)	
occurrences (all)	4	2	
Microalbuminuria			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Nephrectasia			

subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Nephropathy			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Nephrotic syndrome			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Nocturia			
subjects affected / exposed	2 / 200 (1.00%)	2 / 201 (1.00%)	
occurrences (all)	2	2	
Obstructive uropathy			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Oliguria			
subjects affected / exposed	1 / 200 (0.50%)	4 / 201 (1.99%)	
occurrences (all)	1	5	
Pollakiuria			
subjects affected / exposed	2 / 200 (1.00%)	1 / 201 (0.50%)	
occurrences (all)	2	1	
Polyuria			
subjects affected / exposed	3 / 200 (1.50%)	2 / 201 (1.00%)	
occurrences (all)	3	2	
Proteinuria			
subjects affected / exposed	8 / 200 (4.00%)	8 / 201 (3.98%)	
occurrences (all)	8	8	
Pyelocaliectasis			
subjects affected / exposed	2 / 200 (1.00%)	1 / 201 (0.50%)	
occurrences (all)	2	1	
Renal colic			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Renal artery stenosis			
subjects affected / exposed	1 / 200 (0.50%)	2 / 201 (1.00%)	
occurrences (all)	1	2	
Renal failure acute			

subjects affected / exposed	2 / 200 (1.00%)	3 / 201 (1.49%)	
occurrences (all)	2	3	
Renal failure chronic			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Renal glycosuria			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Renal haemorrhage			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Renal impairment			
subjects affected / exposed	5 / 200 (2.50%)	9 / 201 (4.48%)	
occurrences (all)	6	9	
Renal pain			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Renal tubular acidosis			
subjects affected / exposed	1 / 200 (0.50%)	1 / 201 (0.50%)	
occurrences (all)	1	1	
Renal tubular disorder			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Strangury			
subjects affected / exposed	0 / 200 (0.00%)	2 / 201 (1.00%)	
occurrences (all)	0	2	
Ureteric dilatation			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Ureteric stenosis			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Urethral dilatation			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Urethral haemorrhage			

subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Urethral obstruction			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Urethral pain			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Urge incontinence			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Urinary bladder polyp			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Urinary incontinence			
subjects affected / exposed	2 / 200 (1.00%)	3 / 201 (1.49%)	
occurrences (all)	2	3	
Urinary retention			
subjects affected / exposed	2 / 200 (1.00%)	3 / 201 (1.49%)	
occurrences (all)	3	3	
Urinary tract disorder			
subjects affected / exposed	2 / 200 (1.00%)	2 / 201 (1.00%)	
occurrences (all)	2	2	
Urinary tract obstruction			
subjects affected / exposed	1 / 200 (0.50%)	1 / 201 (0.50%)	
occurrences (all)	1	1	
Urinary tract pain			
subjects affected / exposed	2 / 200 (1.00%)	0 / 201 (0.00%)	
occurrences (all)	2	0	
Urinoma			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Hyperparathyroidism secondary			
subjects affected / exposed	2 / 200 (1.00%)	2 / 201 (1.00%)	
occurrences (all)	2	2	

Hyperparathyroidism			
subjects affected / exposed	3 / 200 (1.50%)	0 / 201 (0.00%)	
occurrences (all)	3	0	
Hypoparathyroidism			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Hypothyroidism			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 200 (2.00%)	2 / 201 (1.00%)	
occurrences (all)	4	2	
Back pain			
subjects affected / exposed	8 / 200 (4.00%)	6 / 201 (2.99%)	
occurrences (all)	8	6	
Flank pain			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Groin pain			
subjects affected / exposed	2 / 200 (1.00%)	1 / 201 (0.50%)	
occurrences (all)	2	1	
Intervertebral disc compression			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Joint swelling			
subjects affected / exposed	3 / 200 (1.50%)	1 / 201 (0.50%)	
occurrences (all)	3	1	
Muscle atrophy			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Muscle spasms			
subjects affected / exposed	7 / 200 (3.50%)	3 / 201 (1.49%)	
occurrences (all)	7	3	
Muscular weakness			

subjects affected / exposed	2 / 200 (1.00%)	0 / 201 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 200 (0.50%)	1 / 201 (0.50%)	
occurrences (all)	1	1	
Musculoskeletal pain			
subjects affected / exposed	2 / 200 (1.00%)	2 / 201 (1.00%)	
occurrences (all)	3	2	
Myalgia			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Myopathy			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Neck mass			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Neck pain			
subjects affected / exposed	1 / 200 (0.50%)	2 / 201 (1.00%)	
occurrences (all)	1	2	
Osteopenia			
subjects affected / exposed	3 / 200 (1.50%)	1 / 201 (0.50%)	
occurrences (all)	3	1	
Osteoporosis			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	2 / 200 (1.00%)	5 / 201 (2.49%)	
occurrences (all)	2	5	
Spinal pain			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Tendon pain			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Tendonitis			

subjects affected / exposed	2 / 200 (1.00%)	2 / 201 (1.00%)	
occurrences (all)	2	2	
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Arteriovenous graft site infection			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Asymptomatic bacteriuria			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
BK virus infection			
subjects affected / exposed	11 / 200 (5.50%)	12 / 201 (5.97%)	
occurrences (all)	11	13	
Bacterial disease carrier			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Bacterial infection			
subjects affected / exposed	1 / 200 (0.50%)	1 / 201 (0.50%)	
occurrences (all)	1	1	
Bacteriuria			
subjects affected / exposed	1 / 200 (0.50%)	1 / 201 (0.50%)	
occurrences (all)	1	1	
Bronchitis			
subjects affected / exposed	3 / 200 (1.50%)	4 / 201 (1.99%)	
occurrences (all)	3	4	
Burkholderia cepacia complex infection			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Campylobacter infection			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Candida infection			

subjects affected / exposed	2 / 200 (1.00%)	1 / 201 (0.50%)	
occurrences (all)	2	1	
Cellulitis			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Clostridial infection			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Clostridium difficile colitis			
subjects affected / exposed	2 / 200 (1.00%)	1 / 201 (0.50%)	
occurrences (all)	2	1	
Clostridium difficile infection			
subjects affected / exposed	0 / 200 (0.00%)	2 / 201 (1.00%)	
occurrences (all)	0	2	
Conjunctivitis			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Cystitis escherichia			
subjects affected / exposed	0 / 200 (0.00%)	2 / 201 (1.00%)	
occurrences (all)	0	2	
Cystitis			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Cytomegalovirus infection			
subjects affected / exposed	28 / 200 (14.00%)	28 / 201 (13.93%)	
occurrences (all)	32	29	
Cytomegalovirus viraemia			
subjects affected / exposed	2 / 200 (1.00%)	1 / 201 (0.50%)	
occurrences (all)	3	1	
Device related infection			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Enterobacter bacteraemia			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Enterobacter infection			

subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Enterococcal infection			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Epididymitis			
subjects affected / exposed	0 / 200 (0.00%)	2 / 201 (1.00%)	
occurrences (all)	0	2	
Epstein-Barr virus infection			
subjects affected / exposed	1 / 200 (0.50%)	1 / 201 (0.50%)	
occurrences (all)	1	1	
Escherichia infection			
subjects affected / exposed	1 / 200 (0.50%)	1 / 201 (0.50%)	
occurrences (all)	1	1	
Escherichia urinary tract infection			
subjects affected / exposed	7 / 200 (3.50%)	7 / 201 (3.48%)	
occurrences (all)	7	7	
Folliculitis			
subjects affected / exposed	0 / 200 (0.00%)	2 / 201 (1.00%)	
occurrences (all)	0	2	
Fungal infection			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Gastroenteritis viral			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis			
subjects affected / exposed	3 / 200 (1.50%)	5 / 201 (2.49%)	
occurrences (all)	3	5	
Gastrointestinal infection			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Genital herpes simplex			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Genital herpes			

subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Gingivitis			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Graft infection			
subjects affected / exposed	1 / 200 (0.50%)	2 / 201 (1.00%)	
occurrences (all)	1	2	
Herpes simplex			
subjects affected / exposed	1 / 200 (0.50%)	1 / 201 (0.50%)	
occurrences (all)	1	1	
Herpes virus infection			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Herpes zoster			
subjects affected / exposed	1 / 200 (0.50%)	1 / 201 (0.50%)	
occurrences (all)	1	1	
Human polyomavirus infection			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Influenza			
subjects affected / exposed	2 / 200 (1.00%)	2 / 201 (1.00%)	
occurrences (all)	2	2	
Keratitis bacterial			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Klebsiella infection			
subjects affected / exposed	3 / 200 (1.50%)	2 / 201 (1.00%)	
occurrences (all)	3	2	
Laryngitis			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	2	
Lung infection			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Nasal herpes			

subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	10 / 200 (5.00%)	4 / 201 (1.99%)	
occurrences (all)	12	4	
Oesophageal candidiasis			
subjects affected / exposed	0 / 200 (0.00%)	2 / 201 (1.00%)	
occurrences (all)	0	2	
Onychomycosis			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Ophthalmic herpes zoster			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Oral candidiasis			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Oral fungal infection			
subjects affected / exposed	0 / 200 (0.00%)	2 / 201 (1.00%)	
occurrences (all)	0	2	
Oral herpes			
subjects affected / exposed	2 / 200 (1.00%)	2 / 201 (1.00%)	
occurrences (all)	5	2	
Oropharyngeal candidiasis			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Otitis media			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Pharyngitis			
subjects affected / exposed	1 / 200 (0.50%)	1 / 201 (0.50%)	
occurrences (all)	1	1	
Pneumonia			
subjects affected / exposed	3 / 200 (1.50%)	1 / 201 (0.50%)	
occurrences (all)	3	1	
Polyomavirus-associated			

nephropathy			
subjects affected / exposed	1 / 200 (0.50%)	1 / 201 (0.50%)	
occurrences (all)	1	1	
Post procedural infection			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Postoperative wound infection			
subjects affected / exposed	2 / 200 (1.00%)	2 / 201 (1.00%)	
occurrences (all)	2	2	
Pseudomonas infection			
subjects affected / exposed	2 / 200 (1.00%)	1 / 201 (0.50%)	
occurrences (all)	2	1	
Pulpitis dental			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Pyelonephritis acute			
subjects affected / exposed	1 / 200 (0.50%)	1 / 201 (0.50%)	
occurrences (all)	1	1	
Pyelonephritis			
subjects affected / exposed	4 / 200 (2.00%)	0 / 201 (0.00%)	
occurrences (all)	5	0	
Pyuria			
subjects affected / exposed	0 / 200 (0.00%)	2 / 201 (1.00%)	
occurrences (all)	0	2	
Rash pustular			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Respiratory tract infection			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Rotavirus infection			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Sinusitis			
subjects affected / exposed	2 / 200 (1.00%)	1 / 201 (0.50%)	
occurrences (all)	2	1	

Staphylococcal infection			
subjects affected / exposed	3 / 200 (1.50%)	0 / 201 (0.00%)	
occurrences (all)	3	0	
Streptococcal infection			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Tooth abscess			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	3 / 200 (1.50%)	0 / 201 (0.00%)	
occurrences (all)	3	0	
Ureteritis			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Urethritis			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection bacterial			
subjects affected / exposed	5 / 200 (2.50%)	10 / 201 (4.98%)	
occurrences (all)	5	14	
Urinary tract infection enterococcal			
subjects affected / exposed	3 / 200 (1.50%)	1 / 201 (0.50%)	
occurrences (all)	5	1	
Urinary tract infection pseudomonal			
subjects affected / exposed	3 / 200 (1.50%)	1 / 201 (0.50%)	
occurrences (all)	3	1	
Urinary tract infection viral			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	31 / 200 (15.50%)	22 / 201 (10.95%)	
occurrences (all)	37	23	
Urosepsis			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	

Viral infection			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 200 (0.00%)	2 / 201 (1.00%)	
occurrences (all)	0	2	
Wound infection			
subjects affected / exposed	1 / 200 (0.50%)	1 / 201 (0.50%)	
occurrences (all)	1	1	
Metabolism and nutrition disorders			
Acidosis hyperchloraemic			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Acidosis			
subjects affected / exposed	6 / 200 (3.00%)	3 / 201 (1.49%)	
occurrences (all)	8	3	
Alkalosis			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Calcium deficiency			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Cell death			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Decreased appetite			
subjects affected / exposed	1 / 200 (0.50%)	1 / 201 (0.50%)	
occurrences (all)	1	1	
Dehydration			
subjects affected / exposed	1 / 200 (0.50%)	1 / 201 (0.50%)	
occurrences (all)	1	1	
Diabetes mellitus			

subjects affected / exposed	12 / 200 (6.00%)	20 / 201 (9.95%)	
occurrences (all)	12	20	
Dyslipidaemia			
subjects affected / exposed	6 / 200 (3.00%)	11 / 201 (5.47%)	
occurrences (all)	6	11	
Electrolyte depletion			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Electrolyte imbalance			
subjects affected / exposed	4 / 200 (2.00%)	7 / 201 (3.48%)	
occurrences (all)	5	8	
Fluid overload			
subjects affected / exposed	4 / 200 (2.00%)	4 / 201 (1.99%)	
occurrences (all)	4	4	
Fluid retention			
subjects affected / exposed	12 / 200 (6.00%)	7 / 201 (3.48%)	
occurrences (all)	12	9	
Folate deficiency			
subjects affected / exposed	0 / 200 (0.00%)	4 / 201 (1.99%)	
occurrences (all)	0	4	
Glucose tolerance impaired			
subjects affected / exposed	0 / 200 (0.00%)	3 / 201 (1.49%)	
occurrences (all)	0	3	
Gout			
subjects affected / exposed	1 / 200 (0.50%)	1 / 201 (0.50%)	
occurrences (all)	1	1	
Hypercalcaemia			
subjects affected / exposed	4 / 200 (2.00%)	5 / 201 (2.49%)	
occurrences (all)	4	5	
Hypercholesterolaemia			
subjects affected / exposed	7 / 200 (3.50%)	2 / 201 (1.00%)	
occurrences (all)	7	2	
Hypercreatininaemia			
subjects affected / exposed	3 / 200 (1.50%)	1 / 201 (0.50%)	
occurrences (all)	4	1	
Hyperglycaemia			

subjects affected / exposed	20 / 200 (10.00%)	17 / 201 (8.46%)	
occurrences (all)	22	17	
Hyperkalaemia			
subjects affected / exposed	31 / 200 (15.50%)	29 / 201 (14.43%)	
occurrences (all)	35	37	
Hyperlactacidaemia			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Hyperlipidaemia			
subjects affected / exposed	10 / 200 (5.00%)	13 / 201 (6.47%)	
occurrences (all)	10	13	
Hypernatraemia			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Hyperphosphataemia			
subjects affected / exposed	14 / 200 (7.00%)	8 / 201 (3.98%)	
occurrences (all)	14	8	
Hypertriglyceridaemia			
subjects affected / exposed	1 / 200 (0.50%)	2 / 201 (1.00%)	
occurrences (all)	1	2	
Hyperuricaemia			
subjects affected / exposed	22 / 200 (11.00%)	19 / 201 (9.45%)	
occurrences (all)	23	19	
Hypervolaemia			
subjects affected / exposed	2 / 200 (1.00%)	1 / 201 (0.50%)	
occurrences (all)	2	1	
Hypocalcaemia			
subjects affected / exposed	25 / 200 (12.50%)	17 / 201 (8.46%)	
occurrences (all)	26	17	
Hypoglycaemia			
subjects affected / exposed	0 / 200 (0.00%)	2 / 201 (1.00%)	
occurrences (all)	0	2	
Hypokalaemia			
subjects affected / exposed	22 / 200 (11.00%)	27 / 201 (13.43%)	
occurrences (all)	25	29	
Hypomagnesaemia			

subjects affected / exposed	22 / 200 (11.00%)	9 / 201 (4.48%)	
occurrences (all)	22	9	
Hyponatraemia			
subjects affected / exposed	4 / 200 (2.00%)	4 / 201 (1.99%)	
occurrences (all)	4	4	
Hypophosphataemia			
subjects affected / exposed	18 / 200 (9.00%)	11 / 201 (5.47%)	
occurrences (all)	18	11	
Hypovitaminosis			
subjects affected / exposed	1 / 200 (0.50%)	3 / 201 (1.49%)	
occurrences (all)	1	3	
Hypovolaemia			
subjects affected / exposed	2 / 200 (1.00%)	2 / 201 (1.00%)	
occurrences (all)	2	2	
Increased appetite			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Iron deficiency			
subjects affected / exposed	1 / 200 (0.50%)	5 / 201 (2.49%)	
occurrences (all)	1	5	
Magnesium deficiency			
subjects affected / exposed	4 / 200 (2.00%)	4 / 201 (1.99%)	
occurrences (all)	5	5	
Malnutrition			
subjects affected / exposed	1 / 200 (0.50%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Metabolic acidosis			
subjects affected / exposed	15 / 200 (7.50%)	12 / 201 (5.97%)	
occurrences (all)	15	12	
Obesity			
subjects affected / exposed	1 / 200 (0.50%)	1 / 201 (0.50%)	
occurrences (all)	1	1	
Overweight			
subjects affected / exposed	0 / 200 (0.00%)	1 / 201 (0.50%)	
occurrences (all)	0	1	
Type 2 diabetes mellitus			

subjects affected / exposed	3 / 200 (1.50%)	1 / 201 (0.50%)	
occurrences (all)	3	1	
Vitamin D deficiency			
subjects affected / exposed	3 / 200 (1.50%)	4 / 201 (1.99%)	
occurrences (all)	3	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 March 2015	·Clarify the study rationale · Clarify timing of tacrolimus first dosing · Allow dispensation of new dosage instructions and study drugs to the patients, the day after the scheduled visit · Introduce BAASIS questionnaire · Add Pharmacovigilance contact details · Make other minor typographic, grammatical and administrative changes as necessary
01 September 2015	• Allow dispensation of new dosage instructions to the patients over the phone; • Introduce Norvegian BAASIS questionnaire; • Introduce the possibility to detect either Urea or BUN to check the kidney functionality; • Update of the denomination of the role of CHIESI Pharmacovigilance referent.
11 April 2016	• Clarify that randomization before transplantation is allowed • Clarified that "current PRA" refers to the last PRA of a patient on the waiting list determined within 3 months before transplantation • Clarify methods allowed for anti-HLA Panel Reactive Antibody evaluation • Introduce the possibility to perform the urinalyses either with quantitative method or with dipstick;

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported