



## 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
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#### 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 Trasparenzy, Clinical Trial Trasparenzy, clinicaltrials_info@chiesi.com
Scientific contact	Clinical Trial Trasparenzy, Clinical Trial Trasparenzy, 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:

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### 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.

<b>Arm title</b>	2_Prograf® /Advagraf®
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**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.

<b>Number of subjects in period 1<sup>[1]</sup></b>	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

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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®
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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®
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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 <sup>[1]</sup>	194 <sup>[2]</sup>		
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



<b>Statistical analysis title</b>	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 <sup>[3]</sup>
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 <sup>[4]</sup>	194 <sup>[5]</sup>		
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

<b>Statistical analysis title</b>	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 <sup>[6]</sup>
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
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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
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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 <sup>[7]</sup>	201 <sup>[8]</sup>		
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

<b>Statistical analysis title</b>	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 <sup>[9]</sup>
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

<b>Statistical analysis title</b>	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 <sup>[10]</sup>
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

<b>Statistical analysis title</b>	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 <sup>[11]</sup>
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

<b>Statistical analysis title</b>	4_Treatment Failure Rate_overall_BPAR
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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 <sup>[12]</sup>
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
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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
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End point timeframe:

from the randomization day +1.

<b>End point values</b>	1_Envarsus®	2_Prograf® /Advagraf®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	200 <sup>[13]</sup>	201 <sup>[14]</sup>		
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

<b>Statistical analysis title</b>	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

<b>End point title</b>	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 <sup>[15]</sup>	201 <sup>[16]</sup>		
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
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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 <sup>[17]</sup>
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
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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
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End point timeframe:

overall the study

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

Notes:

[18] - N=200;n=200

[19] - N=201;n=201

## Statistical analyses

<b>Statistical analysis title</b>	1_Local diagnosis Acute Rejection requiring treat.
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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 <sup>[20]</sup>
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)
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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])

Nºof 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
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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 <sup>[21]</sup>	201 <sup>[22]</sup>		
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
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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 <sup>[23]</sup>
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
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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®
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Number of subjects included in analysis	401
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.749 <sup>[24]</sup>
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:	
<p>Safety endpoint.</p> <p>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 <math>\geq 126</math> mg/dL, and/or for subjects with no prior medical history of diabetes, an afternoon capillary glucose level of <math>\geq 200</math> mg/dL with or without insulin requirement or need for an oral hypoglycaemic agent</p> <p>Shown are the number of patients included in the model (safety population [N]; patients with available results [n])</p> <p>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.</p>	
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 <sup>[25]</sup>	201 <sup>[26]</sup>		
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
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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 <sup>[27]</sup>
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

<b>Statistical analysis title</b>	2_PTH_month 6
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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 <sup>[28]</sup>
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)
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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
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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 <sup>[29]</sup>	201 <sup>[30]</sup>		
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
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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
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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 <sup>[31]</sup>	201 <sup>[32]</sup>		
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

<b>Statistical analysis title</b>	1_TDD_overall
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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 <sup>[33]</sup>
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.

<b>Statistical analysis title</b>	2_TDD_week1
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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

<b>Statistical analysis title</b>	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

<b>Statistical analysis title</b>	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

<b>Statistical analysis title</b>	5_TDD_week4
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**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

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**Statistical analysis title**

6\_TDD\_month 1 to month 3

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**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

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**Statistical analysis title**

7\_TDD\_month 3 to month 6

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**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 <sup>[34]</sup>	201 <sup>[35]</sup>		
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 performed 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:	
<ul style="list-style-type: none"> <li>- herpes simplex virus (HSV),</li> <li>- varicella zoster virus (VZV),</li> <li>- Epstein-Barr virus (EBV),</li> <li>- Cytomegalovirus (CMV),</li> <li>- PcP (Pneumocystitis jiroveci pneumonia)</li> <li>- Mycobacterium tuberculosis</li> <li>- Toxoplasma gondii</li> <li>- Nocardia species</li> <li>- Listeria monocytogenes infections</li> <li>- fungi.</li> </ul>	
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 <sup>[36]</sup>	201 <sup>[37]</sup>		
Units: number of subject				
subjects	38	40		

Notes:

[36] - N=200;n=200

[37] - N=201;n=201

## Statistical analyses

<b>Statistical analysis title</b>	1_opportunistic 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 <sup>[38]</sup>
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 <sup>[39]</sup>	201 <sup>[40]</sup>		
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

<b>Statistical analysis title</b>	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 <sup>[41]</sup>
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 <sup>[42]</sup>	201 <sup>[43]</sup>		
Units: number of subject				
subjects	1	3		

Notes:

[42] - N=200;n=200

[43] - N=201;n=201

## Statistical analyses

<b>Statistical analysis title</b>	1_malignancy
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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 <sup>[44]</sup>
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 <sup>[45]</sup>	201 <sup>[46]</sup>		
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

<b>Statistical analysis title</b>	3_eGFR_day 120
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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

<b>Statistical analysis title</b>	4_eGFR_day 150
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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

<b>Statistical analysis title</b>	5_eGFR_day 180
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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
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.1
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### Reporting groups

Reporting group title	1_Envarsus®
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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®
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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	
<b>Hypocalcaemia</b>			
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	
<b>Hyponatraemia</b>			
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	
<b>Metabolic acidosis</b>			
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 %

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

Vulvovaginal warts subjects affected / exposed occurrences (all)	0 / 200 (0.00%) 0	1 / 201 (0.50%) 1	
Vascular disorders			
Aortic aneurysm subjects affected / exposed occurrences (all)	0 / 200 (0.00%) 0	1 / 201 (0.50%) 1	
Arterial disorder subjects affected / exposed occurrences (all)	0 / 200 (0.00%) 0	1 / 201 (0.50%) 1	
Arteriovenous fistula subjects affected / exposed occurrences (all)	1 / 200 (0.50%) 1	0 / 201 (0.00%) 0	
Deep vein thrombosis subjects affected / exposed occurrences (all)	2 / 200 (1.00%) 2	3 / 201 (1.49%) 3	
Haematoma subjects affected / exposed occurrences (all)	3 / 200 (1.50%) 3	2 / 201 (1.00%) 2	
Hot flush subjects affected / exposed occurrences (all)	0 / 200 (0.00%) 0	1 / 201 (0.50%) 1	
Hypertension subjects affected / exposed occurrences (all)	39 / 200 (19.50%) 41	29 / 201 (14.43%) 30	
Hypertensive crisis subjects affected / exposed occurrences (all)	2 / 200 (1.00%) 2	2 / 201 (1.00%) 3	
Hypotension subjects affected / exposed occurrences (all)	8 / 200 (4.00%) 8	6 / 201 (2.99%) 6	
Intra-abdominal haematoma subjects affected / exposed occurrences (all)	3 / 200 (1.50%) 3	0 / 201 (0.00%) 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 occurrences (all)	21 / 200 (10.50%) 23	9 / 201 (4.48%) 11	
Xerosis subjects affected / exposed occurrences (all)	1 / 200 (0.50%) 1	0 / 201 (0.00%) 0	
Immune system disorders Drug hypersensitivity subjects affected / exposed occurrences (all)	1 / 200 (0.50%) 1	0 / 201 (0.00%) 0	
Hypogammaglobulinaemia subjects affected / exposed occurrences (all)	1 / 200 (0.50%) 1	0 / 201 (0.00%) 0	
Seasonal allergy subjects affected / exposed occurrences (all)	1 / 200 (0.50%) 1	0 / 201 (0.00%) 0	
Transplant rejection subjects affected / exposed occurrences (all)	9 / 200 (4.50%) 10	4 / 201 (1.99%) 4	
Reproductive system and breast disorders Benign prostatic hyperplasia subjects affected / exposed occurrences (all)	1 / 200 (0.50%) 1	6 / 201 (2.99%) 6	
Breast mass subjects affected / exposed occurrences (all)	0 / 200 (0.00%) 0	1 / 201 (0.50%) 1	
Dysmenorrhoea subjects affected / exposed occurrences (all)	1 / 200 (0.50%) 1	0 / 201 (0.00%) 0	
Erectile dysfunction subjects affected / exposed occurrences (all)	1 / 200 (0.50%) 1	1 / 201 (0.50%) 1	
Gynaecomastia subjects affected / exposed occurrences (all)	0 / 200 (0.00%) 0	1 / 201 (0.50%) 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 occurrences (all)	3 / 200 (1.50%) 3	2 / 201 (1.00%) 2	
Pulmonary venous thrombosis subjects affected / exposed occurrences (all)	1 / 200 (0.50%) 1	0 / 201 (0.00%) 0	
Rales subjects affected / exposed occurrences (all)	0 / 200 (0.00%) 0	1 / 201 (0.50%) 1	
Respiratory failure subjects affected / exposed occurrences (all)	1 / 200 (0.50%) 1	0 / 201 (0.00%) 0	
Rhinorrhoea subjects affected / exposed occurrences (all)	1 / 200 (0.50%) 1	0 / 201 (0.00%) 0	
Sinus congestion subjects affected / exposed occurrences (all)	1 / 200 (0.50%) 1	0 / 201 (0.00%) 0	
Sputum increased subjects affected / exposed occurrences (all)	0 / 200 (0.00%) 0	1 / 201 (0.50%) 1	
Throat irritation subjects affected / exposed occurrences (all)	0 / 200 (0.00%) 0	1 / 201 (0.50%) 1	
Wheezing subjects affected / exposed occurrences (all)	1 / 200 (0.50%) 1	0 / 201 (0.00%) 0	
Psychiatric disorders			
Agitation subjects affected / exposed occurrences (all)	1 / 200 (0.50%) 1	4 / 201 (1.99%) 4	
Anxiety disorder subjects affected / exposed occurrences (all)	0 / 200 (0.00%) 0	1 / 201 (0.50%) 1	
Anxiety subjects affected / exposed occurrences (all)	13 / 200 (6.50%) 13	9 / 201 (4.48%) 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 occurrences (all)	0 / 200 (0.00%) 0	2 / 201 (1.00%) 2	
Renal function test abnormal subjects affected / exposed occurrences (all)	1 / 200 (0.50%) 1	1 / 201 (0.50%) 1	
Staphylococcus test positive subjects affected / exposed occurrences (all)	0 / 200 (0.00%) 0	2 / 201 (1.00%) 2	
Transaminases increased subjects affected / exposed occurrences (all)	2 / 200 (1.00%) 2	2 / 201 (1.00%) 2	
Viral test positive subjects affected / exposed occurrences (all)	1 / 200 (0.50%) 1	0 / 201 (0.00%) 0	
Volume blood decreased subjects affected / exposed occurrences (all)	1 / 200 (0.50%) 1	0 / 201 (0.00%) 0	
Weight decreased subjects affected / exposed occurrences (all)	0 / 200 (0.00%) 0	2 / 201 (1.00%) 2	
Weight increased subjects affected / exposed occurrences (all)	3 / 200 (1.50%) 3	3 / 201 (1.49%) 3	
White blood cell count decreased subjects affected / exposed occurrences (all)	0 / 200 (0.00%) 0	3 / 201 (1.49%) 3	
Injury, poisoning and procedural complications			
Anaemia postoperative subjects affected / exposed occurrences (all)	1 / 200 (0.50%) 1	0 / 201 (0.00%) 0	
Anaesthetic complication subjects affected / exposed occurrences (all)	0 / 200 (0.00%) 0	1 / 201 (0.50%) 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 occurrences (all)	0 / 200 (0.00%) 0	2 / 201 (1.00%) 2	
Subcutaneous haematoma subjects affected / exposed occurrences (all)	2 / 200 (1.00%) 2	0 / 201 (0.00%) 0	
Toxicity to various agents subjects affected / exposed occurrences (all)	2 / 200 (1.00%) 2	2 / 201 (1.00%) 2	
Transplant dysfunction subjects affected / exposed occurrences (all)	1 / 200 (0.50%) 1	0 / 201 (0.00%) 0	
Transplantation complication subjects affected / exposed occurrences (all)	0 / 200 (0.00%) 0	1 / 201 (0.50%) 1	
Wound complication subjects affected / exposed occurrences (all)	9 / 200 (4.50%) 10	17 / 201 (8.46%) 17	
Wound dehiscence subjects affected / exposed occurrences (all)	1 / 200 (0.50%) 1	1 / 201 (0.50%) 1	
Wound haematoma subjects affected / exposed occurrences (all)	0 / 200 (0.00%) 0	2 / 201 (1.00%) 2	
Congenital, familial and genetic disorders			
Hydrocele subjects affected / exposed occurrences (all)	2 / 200 (1.00%) 2	2 / 201 (1.00%) 2	
Hypertrophic cardiomyopathy subjects affected / exposed occurrences (all)	0 / 200 (0.00%) 0	1 / 201 (0.50%) 1	
Cardiac disorders			
Angina pectoris subjects affected / exposed occurrences (all)	3 / 200 (1.50%) 3	4 / 201 (1.99%) 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 occurrences (all)	1 / 200 (0.50%) 1	0 / 201 (0.00%) 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 occurrences (all)	1 / 200 (0.50%) 1	0 / 201 (0.00%) 0	
Vision blurred subjects affected / exposed occurrences (all)	0 / 200 (0.00%) 0	1 / 201 (0.50%) 1	
Visual impairment subjects affected / exposed occurrences (all)	1 / 200 (0.50%) 1	0 / 201 (0.00%) 0	
Vitreous detachment subjects affected / exposed occurrences (all)	1 / 200 (0.50%) 1	0 / 201 (0.00%) 0	
Gastrointestinal disorders			
Abdominal discomfort subjects affected / exposed occurrences (all)	2 / 200 (1.00%) 2	0 / 201 (0.00%) 0	
Abdominal distension subjects affected / exposed occurrences (all)	3 / 200 (1.50%) 3	2 / 201 (1.00%) 2	
Abdominal hernia subjects affected / exposed occurrences (all)	0 / 200 (0.00%) 0	2 / 201 (1.00%) 2	
Abdominal pain upper subjects affected / exposed occurrences (all)	5 / 200 (2.50%) 5	1 / 201 (0.50%) 1	
Abdominal pain subjects affected / exposed occurrences (all)	19 / 200 (9.50%) 20	21 / 201 (10.45%) 21	
Abdominal wall haematoma subjects affected / exposed occurrences (all)	2 / 200 (1.00%) 2	0 / 201 (0.00%) 0	
Abnormal faeces subjects affected / exposed occurrences (all)	0 / 200 (0.00%) 0	1 / 201 (0.50%) 1	
Anal fissure subjects affected / exposed occurrences (all)	1 / 200 (0.50%) 1	0 / 201 (0.00%) 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	
Hypertransaminaemia			
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 occurrences (all)	2 / 200 (1.00%) 2	2 / 201 (1.00%) 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 hyperchloaemic			
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	<ul style="list-style-type: none"><li>· Clarify the study rationale</li><li>· Clarify timing of tacrolimus first dosing</li><li>· Allow dispensation of new dosage instructions and study drugs to the patients, the day after the scheduled visit</li><li>· Introduce BAASIS questionnaire</li><li>· Add Pharmacovigilance contact details</li><li>· Make other minor typographic, grammatical and administrative changes as necessary</li></ul>
01 September 2015	<ul style="list-style-type: none"><li>• Allow dispensation of new dosage instructions to the patients over the phone;</li><li>• Introduce Norwegian BAASIS questionnaire;</li><li>• Introduce the possibility to detect either Urea or BUN to check the kidney functionality;</li><li>• Update of the denomination of the role of CHIESI Pharmacovigilance referent.</li></ul>
11 April 2016	<ul style="list-style-type: none"><li>• Clarify that randomization before transplantation is allowed</li><li>• Clarified that "current PRA" refers to the last PRA of a patient on the waiting list determined within 3 months before transplantation</li><li>• Clarify methods allowed for anti-HLA Panel Reactive Antibody evaluation</li><li>• Introduce the possibility to perform the urinalyses either with quantitative method or with dipstick;</li></ul>

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported