Clinical trial results:
A 3-month, multicenter, randomized, open label study to evaluate the impact of early vs. delayed introduction of everolimus on wound healing in de novo kidney transplant recipients with a follow-up evaluation at 12 months after transplant (NEVERWOUND)

Summary

EudraCT number	2011-002866-19
Trial protocol	IT
Global end of trial date	10 December 2015

Results information

Result version number	v2 (current)
This version publication date	05 July 2017
First version publication date	07 December 2016
Version creation reason	• New data added to full data set 1) End point descriptions for primary end point 1 and secondary end point 1 need to be updated. 2) Data for the month 12 time frame of secondary end point: percentage of participants with BPAR - worst case scenario need to be added.

Trial information

Trial identification

Sponsor protocol code	CRAD001AIT25

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01410448
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma, AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma, AG, 41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma, AG, 41 613241111,

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	10 December 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 December 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to compare the incidence of surgical wound complications (lymphorrhea, fluid collection, incisional hernia, wound dehiscence, wound infections) in the first three months following renal transplant between patients treated with everolimus immediately after transplantation (IE) with those treated 28 ± 4 days later (delayed everolimus - DE).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 November 2011
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	Italy: 383
Worldwide total number of subjects	383
EEA total number of subjects	383

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	328
From 65 to 84 years	55
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study included a 3 month treatment period followed by an observational follow-up period. Participants were treated as per local practice during follow-up and a follow-up evaluation was performed at 12 months.

Pre-assignment

Screening details:

Participants were randomized in a 1:1 ratio to one of the 2 treatment groups.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Immediate Everolimus (IE)

Arm description:

Everolimus was started within 48 hours after graft reperfusion at a starting dose of 0.75 mg twice daily in combination with low-dose cyclosporine and steroids for 3 months.

Arm type	Experimental
Investigational medicinal product name	Everolimus
Investigational medicinal product code	RAD001
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Everolimus was started within 48 hours after graft reperfusion at a starting dose of 0.75 mg twice daily in combination with low-dose cyclosporine and steroids for 3 months.

Arm title	Delayed Everolimus (DE)

Arm description:

The standard dose of mycophenolate sodium was administered within 48 hours after graft reperfusion in combination with a full dose of cyclosporine and steroids. After28 +/- 4 days of treatment, mycophenolate sodium was discontinued and everolimus was introduced at a starting dose of 0.75 mg twice daily for 3 months.

Arm type	Experimental
Investigational medicinal product name	Everolimus
Investigational medicinal product code	RAD001
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The standard dose of mycophenolate sodium was administered within 48 hours after graft reperfusion in combination with a full dose of cyclosporine and steroids. After28 +/- 4 days of treatment, mycophenolate sodium was discontinued and everolimus was introduced at a starting dose of 0.75 mg twice daily for 3 months.

Number of subjects in period 1	Immediate Everolimus (IE)	Delayed Everolimus (DE)
Started	193	190
Intent-to treat (ITT) analysis set	193	190
modified ITT analysis set	161 [1]	149 [2]
Completed	181	155
Not completed	12	35
Adverse event, serious fatal	2	3
Consent withdrawn by subject	3	2
Graft loss	4	1
Administrative issues	2	1
No conversion to everolimus	-	24
Lost to follow-up	1	-
Protocol deviation	-	4

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The number of subjects is correct.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The number of subjects is correct.

Baseline characteristics

Reporting groups	
Reporting group title	Immediate Everolimus (IE)
Reporting group description:	
Everolimus was started within 48 hours after graft reperfusion at a starting dose of 0.75 mg twice daily in combination with low-dose cyclosporine and steroids for 3 months.	
Reporting group title	Delayed Everolimus (DE)
Reporting group description:	
The standard dose of mycophenolate sodium was administered within 48 hours after graft reperfusion in combination with a full dose of cyclosporine and steroids. After28 +/- 4 days of treatment, mycophenolate sodium was discontinued and everolimus was introduced at a starting dose of 0.75 mg twice daily for 3 months.	

Reporting group values	Immediate Everolimus (IE)	Delayed Everolimus (DE)	Total
Number of subjects	193	190	383
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	165	163	328
From 65-84 years	28	27	55
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	51.46	51.19	
standard deviation	± 11.37	± 12.29	-
Gender, Male/Female Units: Subjects			
Female	59	58	117
Male	134	132	266

End points

End points reporting groups

Reporting group title	Immediate Everolimus (IE)
Reporting group description:	
Everolimus was started within 48 hours after graft reperfusion at a starting dose of 0.75 mg twice daily in combination with low-dose cyclosporine and steroids for 3 months.	
Reporting group title	Delayed Everolimus (DE)
Reporting group description:	
The standard dose of mycophenolate sodium was administered within 48 hours after graft reperfusion in combination with a full dose of cyclosporine and steroids. After28 +/- 4 days of treatment, mycophenolate sodium was discontinued and everolimus was introduced at a starting dose of 0.75 mg twice daily for 3 months.	

Primary: Percentage of participants without wound healing complications - Worst-case scenario

End point title	Percentage of participants without wound healing complications - Worst-case scenario
End point description:	
The percentage of participants without wound healing complication was assessed. Wound healing complications consisted of lymphorrhea, fluid collections, wound dehiscence, wound infections and incisional hernia. In the worst-case scenario, failure, i.e. at least one healing complication occurrence, was identified in one of the following cases: wound complication occurrence, missing information about wound complication occurrence, or study discontinuation due to any reason.	
End point type	Primary
End point timeframe:	
3 months	

End point values	Immediate Everolimus (IE)	Delayed Everolimus (DE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	190		
Units: Percentage of participants				
number (not applicable)	68.39	61.58		

Statistical analyses

Statistical analysis title	Complication-free wound healing
Comparison groups	Delayed Everolimus (DE) v Immediate Everolimus (IE)
Number of subjects included in analysis	383
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0921
Method	Regression, Logistic

Secondary: Percentage of participants without wound healing complications - Worst-case scenario

End point title	Percentage of participants without wound healing complications - Worst-case scenario

End point description:

The percentage of participants without wound healing complication was assessed. Wound healing complications consisted of lymphorrhea, fluid collections, wound dehiscence, wound infections and incisional hernia. In the worst-case scenario, failure, i.e. at least one healing complication occurrence, was identified in one of the following cases: wound complication occurrence, missing information about wound complication occurrence or study discontinuation due to any reason for participants who did not complete the 12 month follow-up visit.

End point type	Secondary

End point timeframe:

12 months

End point values	Immediate Everolimus (IE)	Delayed Everolimus (DE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	190		
Units: Percentage of participants				
number (not applicable)	65.8	59.47		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who experienced treatment failure - Worst-case scenario

End point title	Percentage of participants who experienced treatment failure - Worst-case scenario

End point description:

The percentage of participants who experienced treatment failure was assessed. Treatment failure was defined as the occurrence of at least one failure event among death, graft loss or biopsy-proven acute rejection (BPAR). In the worst-case scenario, treatment failure was identified in one of the following cases: occurrence of at least one treatment failure event or study discontinuation due to any reason.

End point type	Secondary

End point timeframe:

3 months

End point values	Immediate Everolimus (IE)	Delayed Everolimus (DE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	190		
Units: Percentage of participants				
number (not applicable)	11.4	21.05		

Statistical analyses

No statistical analyses for this end point

Secondary: Patient survival rate: percentage of deaths - Worst-case scenario

End point title	Patient survival rate: percentage of deaths - Worst-case scenario

End point description:

The percentage of deaths was assessed. In the worst-case scenario, failure, i.e. death, was identified in one of the following cases: participant's death or study discontinuation due to any reason.

End point type	Secondary

End point timeframe:

3 Months, 12 months

End point values	Immediate Everolimus (IE)	Delayed Everolimus (DE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	190		
Units: Percentage of participants				
number (not applicable)	6.22	18.42		

Statistical analyses

No statistical analyses for this end point

Secondary: Participant/graft survival rate: percentage of participants with failure events of death or graft loss - Worst-case scenario

End point title	Participant/graft survival rate: percentage of participants with failure events of death or graft loss - Worst-case scenario

End point description:

The percentage of participants who experienced death or graft loss was assessed. In the worst-case scenario, failure, i.e. participants death or graft loss, was identified in one of the following cases: occurrence of at least one failure event or study discontinuation due to any reason.

End point type	Secondary

End point timeframe:

3 months

End point values	Immediate Everolimus (IE)	Delayed Everolimus (DE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	190		
Units: Percentage of participants				
number (not applicable)	6.74	18.42		

Statistical analyses

No statistical analyses for this end point

Secondary: Graft survival rate: percentage of participants with graft loss - Worst-case scenario

End point title	Graft survival rate: percentage of participants with graft loss - Worst-case scenario

End point description:

The percentage of participants who experienced graft loss was assessed. In the worst-case scenario, failure, i.e. graft loss, was identified in one of the following cases: occurrence of graft loss or discontinuation due to any reason.

End point type	Secondary

End point timeframe:

3 months, 12 months

End point values	Immediate Everolimus (IE)	Delayed Everolimus (DE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	190		
Units: Percentage of participants				
number (not applicable)				
3 months	6.74	18.42		
12 months	7.25	19.47		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with BPAR - Worst-case scenario

End point title	Percentage of participants with BPAR - Worst-case scenario

End point description:

A biopsy-proven acute rejection was defined as a biopsy graded IA, IB, IIA, IIB or III. In the worst-case scenario, failure, i.e. BPAR, was identified in one of the following cases: occurrence of BPAR or study

discontinuation due to any reason.

End point type	Secondary

End point timeframe:

3 Months, 12 months

End point values	Immediate Everolimus (IE)	Delayed Everolimus (DE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	190		
Units: Percentage of participants				
number (not applicable)				
3 months	11.4	21.05		
12 months	15.54	24.74		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with delayed graft function (DGF) -

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

End point description:

DGF was defined as the need for dialysis in the first week after transplant, excluding Renal Replacement Therapy within the first 24 hours after transplantation.

End point type	Secondary

End point timeframe:

3 Months

End point values	Immediate Everolimus (IE)	Delayed Everolimus (DE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	190		
Units: Percentage of participants				
number (not applicable)	23.83	31.58		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of DGF

End point title	Duration of DGF

End point description:

The duration of DGF was defined as the elapsed time from first to last day of post-transplant dialysis.

End point type	Secondary

End point timeframe:

3 months

End point values	Immediate Everolimus (IE)	Delayed Everolimus (DE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	60		
Units: Days				
median (full range (min-max))	8.5 (1 to 93)	5.5 (1 to 76)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in estimated glomerular filtration rate (eGFR) (calculated with modified diet in renal disease (MDRD)-4 formula - ITT

End point title	Change from baseline in estimated glomerular filtration rate (eGFR) (calculated with modified diet in renal disease (MDRD)-4 formula - ITT

End point description:

Renal function was assessed by measuring serum creatinine and serum urea and by calculating creatinine clearance using the MDRD-4 formula. eGFR = 186.3*(serum creatinine [mg/dL])^-1.154 * (age at screening) -0.203 * (0.742 if female) * (1.21 if African American). A positive change from baseline indicates improvement.

End point type	Secondary

End point timeframe:

baseline, 3 Months

End point values	Immediate Everolimus (IE)	Delayed Everolimus (DE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	187	183		
Units: mL/min				
arithmetic mean (standard deviation)	38.64 (± 22.45)	39.13 (± 21.46)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in estimated glomerular filtration rate (eGFR) (calculated with modified diet in renal disease (MDRD)-4 formula - modified ITT

End point title	Change from baseline in estimated glomerular filtration rate (eGFR) (calculated with modified diet in renal disease (MDRD)-4 formula - modified ITT

End point description:

Renal function was assessed by measuring serum creatinine and serum urea and by calculating creatinine clearance using the MDRD-4 formula. eGFR = 186.3*(serum creatinine [mg/dL])^-1.154 * (age at screening) -0.203 * (0.742 if female) * (1.21 if African American). A positive change from baseline indicates improvement.

End point type	Secondary

End point timeframe:

baseline, 12 months

End point values	Immediate Everolimus (IE)	Delayed Everolimus (DE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151	142		
Units: mL/min				
arithmetic mean (standard deviation)	41.26 (± 18.69)	41.56 (± 19.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in serum creatinine - ITT

End point title	Change from baseline in serum creatinine - ITT

End point description:

Blood samples were collected to assess serum creatinine measurements. A negative change from baseline indicates improvement.

End point type	Secondary

End point timeframe:

baseline, 3 months

End point values	Immediate Everolimus (IE)	Delayed Everolimus (DE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	187	183		
Units: mg/dL				
arithmetic mean (standard deviation)	-4.79 (± 2.74)	-5.13 (± 2.32)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in serum creatinine - modified ITT

End point title	Change from baseline in serum creatinine - modified ITT

End point description:

Blood samples were collected to assess serum creatinine measurements. A negative change from baseline indicates improvement.

End point type	Secondary

End point timeframe:

baseline, 12 months

End point values	Immediate Everolimus (IE)	Delayed Everolimus (DE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	150	141		
Units: mg/dL				
arithmetic mean (standard deviation)	-4.96 (± 2.48)	-5.22 (± 2.24)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with proteinuria

End point title	Percentage of participants with proteinuria

End point description:

Incidence of proteinuria (>1,000 mg/day in urine collected in 24 hours or > 1.0 if measured on the urine protein/creatinine concentration ratio in a spot urine sample) was assessed.

End point type	Secondary

End point timeframe:

3 months

End point values	Immediate Everolimus (IE)	Delayed Everolimus (DE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	190		
Units: Percentage of participants				
number (not applicable)				
Yes	4.15	4.21		
No	68.91	68.42		
Missing	26.94	27.37		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with acute rejection (AR)

End point title	Percentage of participants with acute rejection (AR)

End point description:

AR was defined as an episode of increased serum creatinine >30% that was clinically diagnosed as an acute rejection but was not biopsy proven.

End point type	Secondary

End point timeframe:

12 months

End point values	Immediate Everolimus (IE)	Delayed Everolimus (DE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	190		
Units: Percentage of participants				
number (not applicable)	12.44	10.53		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with a new onset of malignancy

End point title	Percentage of participants with a new onset of malignancy

End point description:

The percentage of participants with a new onset of malignancy was assessed.

End point type	Secondary

End point timeframe:

12 months

End point values	Immediate Everolimus (IE)	Delayed Everolimus (DE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	147		
Units: Percentage of participants				
number (not applicable)	0	0.68		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with a new onset of diabetes

End point title	Percentage of participants with a new onset of diabetes

End point description:

The percentage of participants with a new onset of diabetes was assessed.

End point type	Secondary

End point timeframe:

12 months

End point values	Immediate Everolimus (IE)	Delayed Everolimus (DE)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	148		
Units: Percentage of participants				
number (not applicable)	3.14	4.05		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Delayed Everolimus
Reporting group description:	
Delayed Everolimus	
Reporting group title	Immediate Everolimus
Reporting group description:	
Immediate Everolimus	

Serious adverse events	Delayed Everolimus	Immediate Everolimus	
Total subjects affected by serious adverse events			
subjects affected / exposed	61 / 190 (32.11%)	73 / 193 (37.82%)	
number of deaths (all causes)	3	2	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Renal cancer			
subjects affected / exposed	1 / 190 (0.53%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Arterial thrombosis			
subjects affected / exposed	1 / 190 (0.53%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			

subjects affected / exposed	1 / 190 (0.53%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haematoma			
subjects affected / exposed	1 / 190 (0.53%)	3 / 193 (1.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	1 / 190 (0.53%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 190 (0.53%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphocele			
subjects affected / exposed	7 / 190 (3.68%)	7 / 193 (3.63%)	
occurrences causally related to treatment / all	1 / 7	5 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphorrhoea			
subjects affected / exposed	2 / 190 (1.05%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock			
subjects affected / exposed	1 / 190 (0.53%)	0 / 193 (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	0 / 190 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			

subjects affected / exposed	1 / 190 (0.53%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	0 / 190 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	0 / 190 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Bladder catheter replacement			
subjects affected / exposed	0 / 190 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphocele marsupialisation			
subjects affected / exposed	1 / 190 (0.53%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Impaired healing			
subjects affected / exposed	0 / 190 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperpyrexia			
subjects affected / exposed	1 / 190 (0.53%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	1 / 190 (0.53%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Oedema			
subjects affected / exposed	1 / 190 (0.53%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 190 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 190 (0.53%)	3 / 193 (1.55%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Autoimmune disorder			
subjects affected / exposed	1 / 190 (0.53%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney transplant rejection			
subjects affected / exposed	4 / 190 (2.11%)	11 / 193 (5.70%)	
occurrences causally related to treatment / all	0 / 4	4 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transplant rejection			
subjects affected / exposed	1 / 190 (0.53%)	3 / 193 (1.55%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 190 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 190 (0.53%)	0 / 193 (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 / 190 (0.53%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	5 / 190 (2.63%)	4 / 193 (2.07%)	
occurrences causally related to treatment / all	0 / 5	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	1 / 190 (0.53%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Complications of transplanted kidney			
subjects affected / exposed	3 / 190 (1.58%)	2 / 193 (1.04%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Expired product administered			
subjects affected / exposed	0 / 190 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 190 (0.53%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft thrombosis			
subjects affected / exposed	2 / 190 (1.05%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft loss			
subjects affected / exposed	1 / 190 (0.53%)	3 / 193 (1.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Incisional hernia			
subjects affected / exposed	1 / 190 (0.53%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perinephric collection			
subjects affected / exposed	0 / 190 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perirenal haematoma			
subjects affected / exposed	1 / 190 (0.53%)	2 / 193 (1.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	0 / 190 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal haematoma			
subjects affected / exposed	0 / 190 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal transplant failure			
subjects affected / exposed	0 / 190 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous haematoma			
subjects affected / exposed	0 / 190 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	0 / 190 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric anastomosis complication			

subjects affected / exposed	0 / 190 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	2 / 190 (1.05%)	2 / 193 (1.04%)	
occurrences causally related to treatment / all	0 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Protein S deficiency			
subjects affected / exposed	0 / 190 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 190 (0.53%)	2 / 193 (1.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac arrest			
subjects affected / exposed	0 / 190 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiomyopathy			
subjects affected / exposed	1 / 190 (0.53%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 190 (0.53%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Myocardial ischaemia			
subjects affected / exposed	1 / 190 (0.53%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nervous system disorders			
Ataxia			
subjects affected / exposed	0 / 190 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 190 (0.53%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coma			
subjects affected / exposed	0 / 190 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 190 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tremor			
subjects affected / exposed	0 / 190 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 190 (1.05%)	3 / 193 (1.55%)	
occurrences causally related to treatment / all	0 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolytic anaemia			
subjects affected / exposed	1 / 190 (0.53%)	0 / 193 (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	3 / 190 (1.58%)	2 / 193 (1.04%)	
occurrences causally related to treatment / all	2 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Thrombocytopenia			
subjects affected / exposed	0 / 190 (0.00%)	3 / 193 (1.55%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 190 (0.53%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 190 (0.53%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 190 (0.53%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised intraabdominal fluid collection			
subjects affected / exposed	0 / 190 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal haemorrhage			
subjects affected / exposed	0 / 190 (0.00%)	2 / 193 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 190 (0.53%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal haemorrhage			
subjects affected / exposed	0 / 190 (0.00%)	2 / 193 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 190 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 190 (0.53%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocholecystis			
subjects affected / exposed	1 / 190 (0.53%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver disorder			
subjects affected / exposed	0 / 190 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 190 (0.00%)	1 / 193 (0.52%)	
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 / 190 (0.53%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oliguria			
subjects affected / exposed	0 / 190 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perinephric effusion			
subjects affected / exposed	0 / 190 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Proteinuria			
subjects affected / exposed	2 / 190 (1.05%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal artery stenosis			
subjects affected / exposed	0 / 190 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal artery thrombosis			
subjects affected / exposed	1 / 190 (0.53%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 190 (0.53%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	2 / 190 (1.05%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	2 / 190 (1.05%)	3 / 193 (1.55%)	
occurrences causally related to treatment / all	0 / 2	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal ischaemia			
subjects affected / exposed	0 / 190 (0.00%)	1 / 193 (0.52%)	
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	1 / 190 (0.53%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal vein thrombosis			

subjects affected / exposed	0 / 190 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 190 (0.00%)	1 / 193 (0.52%)	
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	1 / 190 (0.53%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 190 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinoma			
subjects affected / exposed	2 / 190 (1.05%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 190 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic deformity			
subjects affected / exposed	0 / 190 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess			
subjects affected / exposed	0 / 190 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bronchopneumonia			
subjects affected / exposed	1 / 190 (0.53%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	0 / 190 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			
subjects affected / exposed	3 / 190 (1.58%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 190 (0.53%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			
subjects affected / exposed	0 / 190 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterobacter infection			
subjects affected / exposed	0 / 190 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected lymphocele			
subjects affected / exposed	0 / 190 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia infection			
subjects affected / exposed	1 / 190 (0.53%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella infection			

subjects affected / exposed	0 / 190 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	0 / 190 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 190 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 190 (0.53%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 190 (0.53%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal abscess			
subjects affected / exposed	0 / 190 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal abscess			
subjects affected / exposed	1 / 190 (0.53%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 190 (0.53%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			

subjects affected / exposed	1 / 190 (0.53%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urinary tract infection			
subjects affected / exposed	7 / 190 (3.68%)	8 / 193 (4.15%)	
occurrences causally related to treatment / all	5 / 8	2 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	2 / 190 (1.05%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	2 / 190 (1.05%)	3 / 193 (1.55%)	
occurrences causally related to treatment / all	0 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 190 (0.53%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyslipidaemia			
subjects affected / exposed	1 / 190 (0.53%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid overload			
subjects affected / exposed	0 / 190 (0.00%)	2 / 193 (1.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercreatininaemia			
subjects affected / exposed	0 / 190 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic disorder			

subjects affected / exposed	2 / 190 (1.05%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Delayed Everolimus	Immediate Everolimus	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	156 / 190 (82.11%)	155 / 193 (80.31%)	
Injury, poisoning and procedural complications			
Complications of transplanted kidney			
subjects affected / exposed	23 / 190 (12.11%)	26 / 193 (13.47%)	
occurrences (all)	23	26	
Vascular disorders			
Hypertension			
subjects affected / exposed	30 / 190 (15.79%)	34 / 193 (17.62%)	
occurrences (all)	30	36	
Haematoma			
subjects affected / exposed	6 / 190 (3.16%)	12 / 193 (6.22%)	
occurrences (all)	7	12	
Lymphocele			
subjects affected / exposed	33 / 190 (17.37%)	25 / 193 (12.95%)	
occurrences (all)	35	28	
Lymphorrhoea			
subjects affected / exposed	11 / 190 (5.79%)	6 / 193 (3.11%)	
occurrences (all)	11	6	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	58 / 190 (30.53%)	67 / 193 (34.72%)	
occurrences (all)	60	67	
Leukopenia			
subjects affected / exposed	14 / 190 (7.37%)	8 / 193 (4.15%)	
occurrences (all)	14	9	
General disorders and administration site conditions			

Pyrexia			
subjects affected / exposed	14 / 190 (7.37%)	16 / 193 (8.29%)	
occurrences (all)	14	19	
Oedema peripheral			
subjects affected / exposed	14 / 190 (7.37%)	17 / 193 (8.81%)	
occurrences (all)	14	17	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	15 / 190 (7.89%)	14 / 193 (7.25%)	
occurrences (all)	17	14	
Constipation			
subjects affected / exposed	13 / 190 (6.84%)	12 / 193 (6.22%)	
occurrences (all)	13	12	
Nausea			
subjects affected / exposed	14 / 190 (7.37%)	4 / 193 (2.07%)	
occurrences (all)	14	5	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	3 / 190 (1.58%)	14 / 193 (7.25%)	
occurrences (all)	3	14	
Infections and infestations			
Cytomegalovirus infection			
subjects affected / exposed	16 / 190 (8.42%)	13 / 193 (6.74%)	
occurrences (all)	16	14	
Urinary tract infection			
subjects affected / exposed	34 / 190 (17.89%)	34 / 193 (17.62%)	
occurrences (all)	40	45	
Metabolism and nutrition disorders			
Dyslipidaemia			
subjects affected / exposed	24 / 190 (12.63%)	28 / 193 (14.51%)	
occurrences (all)	24	28	
Hyperkalaemia			
subjects affected / exposed	18 / 190 (9.47%)	10 / 193 (5.18%)	
occurrences (all)	18	10	
Hypercholesterolaemia			
subjects affected / exposed	9 / 190 (4.74%)	20 / 193 (10.36%)	
occurrences (all)	9	20	

Hyperlipidaemia			
subjects affected / exposed	10 / 190 (5.26%)	6 / 193 (3.11%)	
occurrences (all)	10	6	
Hyperphosphataemia			
subjects affected / exposed	13 / 190 (6.84%)	20 / 193 (10.36%)	
occurrences (all)	14	20	
Hypertriglyceridaemia			
subjects affected / exposed	9 / 190 (4.74%)	14 / 193 (7.25%)	
occurrences (all)	9	14	
Hyperuricaemia			
subjects affected / exposed	25 / 190 (13.16%)	21 / 193 (10.88%)	
occurrences (all)	25	21	
Hypocalcaemia			
subjects affected / exposed	30 / 190 (15.79%)	24 / 193 (12.44%)	
occurrences (all)	30	24	
Hypokalaemia			
subjects affected / exposed	24 / 190 (12.63%)	26 / 193 (13.47%)	
occurrences (all)	24	26	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 January 2013	Results from the CALLISTO study, a 12-month, randomized, multicenter study comparing de novo everolimus versus de novo MPA, were presented. The CALLISTO study investigated whether the delayed administration of everolimus reduced the incidence of DGF and wound-healing events without compromising efficacy in transplant patients at protocol-specified DGF risk during a 3-month period and then at 1 year post- transplant. After 4 weeks from kidney transplant, the incidence of wound-healing disorders was 24.6% (16/65) and 33.8% (25/74) in the immediate everolimus and delayed everolimus groups respectively (p=0.267). At 3 months and at 1 year, consistent results and similar differences in the incidences of wound-healing complications between treatment groups were observed. Based on these results (about 10% difference), but considering the small population of the CALLISTO study and sample size estimation calculated not only on wound-healingcomplication (the primary objective was a composite endpoint including DGF and wound- healing complications), it was decided to maintain the superiority design but to revise the limit. The expected difference between groups was changed from 20% to 15% since it was considered more adequate as a clinically significant difference in the proportion of patients without wound-healing complications in each group at 3 months after transplant. Consequently, the total number of patients to be enrolled increased from 214 to 396 (i.e. 198 patients in each treatment group). In addition, it was decided to collect more data on long-term wound-healing complications in the two groups. For this reason, an additional follow-up visit at 12 months after transplant was added to the study period stated in the original protocol. At this visit, the safety profile and immunosuppressive therapy used from the end of the study to 12 months after transplantation was to be described as well.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported