



Clinical trial results:

Multi-center, open-label, prospective, randomized, parallel group, long-term study investigating a standard regimen in de novo kidney transplant patients versus a CNI free regimen and a CNI low dose regimen.

Summary

EudraCT number	2006-007021-32
Trial protocol	DE
Global end of trial date	04 June 2015

Results information

Result version number	v1 (current)
This version publication date	23 July 2016
First version publication date	23 July 2016

Trial information

Trial identification

Sponsor protocol code	CRAD001ADE13
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00514514
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	04 June 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 June 2015
Global end of trial reached?	Yes
Global end of trial date	04 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial was to demonstrate superiority of a CNI free regimen with respect to renal function at Month 12 post-transplant assessed by GFR (Nankivell method) as compared to the standard regimen in de novo kidney transplant patients.

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.

Rescue medication was permitted in the following circumstances:

Biopsy-confirmed acute rejection episodes were to be treated with i.v. methylprednisolone at a recommended dose of 500-1000 mg for three days. Infection prophylaxis treatment was permitted for patients at high risk of CMV (a CMV positive donor organ transplanted into a CMV negative recipient). Hyperlipidemia medications to lower lipids (e.g., fluvastatin, Lescol®) were to be administered for patients with increased LDL-cholesterol and triglyceride levels.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 July 2007
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 780
Country: Number of subjects enrolled	Switzerland: 22
Worldwide total number of subjects	802
EEA total number of subjects	780

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)	714
From 65 to 84 years	88
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

817 patients were screened and 802 were enrolled on Day of transplant which served as Baseline Visit 1. For three months post transplantation, in the pre-phase period, all patients received induction therapy (Simulect®) and immunosuppressive therapy consisting of Myfortic, Sandimmun Optoral and corticosteroids.

Pre-assignment

Screening details:

At month 3 post transplant, Baseline Visit 2, additional eligibility was assessed and patients randomized to one of 3 treatment arms and stratified according to kidney donor (living or cadaveric).

Period 1

Period 1 title	Pre-phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Standard regimen - Pre-phase
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Arm description:

Myfortic, Sandimmun Optoral, corticosteroids and Simulect® (if patient received transplant)

Arm type	Standard care
Investigational medicinal product name	Mycophenolate Sodium
Investigational medicinal product code	
Other name	Myfortic
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Tablets containing 180 mg or 360 mg. 1440 mg/day (2 x 720 mg), if tolerated. Dose reduction possible in case of side effects (min. dose at BL2 (Month 3): 720 mg/day). Trade ware was used.

Investigational medicinal product name	Cyclosporine A
Investigational medicinal product code	
Other name	Sandimmun Optoral
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Capsules containing 10, 25, 50 or 100 mg. Dosing was based on C0-h and/or C2-h level.

Investigational medicinal product name	Corticosteroids
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

During the first year after transplant, corticosteroids were added to the immunosuppressive regimen in all patients, according to local standard. A minimum dose of 5 mg prednisolone or equivalent was continued throughout this first year. After the first year, it was the investigators' discretion to prescribe steroids or not.

Investigational medicinal product name	Basiliximab
Investigational medicinal product code	
Other name	Simulect®
Pharmaceutical forms	Concentrate for solution for injection

Routes of administration	Intravenous bolus use
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Dosage and administration details:

Vials containing 20 mg lyophilisate were supplied. 2 x 20 mg to be applied as 10 sec. bolus injection, i.v. on Day 0 (2 h before transplant) and on Day 4. Trade ware was used.

Number of subjects in period 1	Standard regimen - Pre-phase
Started	802
Completed	499
Not completed	303
Adverse event, serious fatal	10
condition no longer requires study drug	7
Consent withdrawn by subject	66
Adverse event, non-fatal	137
Administrative problems	2
abnormal lab values	23
abnormal test procedure results	15
Lost to follow-up	2
Protocol deviation	6
Lack of efficacy	35

Period 2

Period 2 title	Randomized - 9 Month
Is this the baseline period?	Yes ^[1]
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Standard regimen

Arm description:

Myfortic, Sandimmun Optoral and corticosteroids

Arm type	Active comparator
Investigational medicinal product name	Mycophenolate Sodium
Investigational medicinal product code	
Other name	Myfortic
Pharmaceutical forms	Capsule, Coated tablet
Routes of administration	Oral use

Dosage and administration details:	
Tablets containing 180 mg or 360 mg. 1440 mg/day (2 x 720 mg), if tolerated. Dose reduction possible in case of side effects (min. dose at BL2 (Month 3): 720 mg/day). Trade ware was used.	
Investigational medicinal product name	Corticosteroids
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

During the first year after transplant, corticosteroids were added to the immunosuppressive regimen in all patients, according to local standard. A minimum dose of 5 mg prednisolone or equivalent was continued throughout this first year. After the first year, it was the investigators' discretion to prescribe steroids or not.

Investigational medicinal product name	Cyclosporine A
Investigational medicinal product code	
Other name	Sandimmun Optoral
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Capsules containing 10,25,50 or 100 mg. Dosing was based on C0-h and/or C2-h level.

Arm title	CNI free regimen
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Arm description:

CNI free regimen: comprising the following steps for switching treatment: Step 1 at BL2 + 1 day: Myfortic, Certican 1.5 mg, Sandimmun Optoral (50% of standard dose) and corticosteroids Step 2 at BL2 + 8 days: Myfortic, Certican 3 mg and corticosteroids

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

Dosage and administration details:

Initially 1.5 mg/day, then based on blood levels (5-10 ng/mL in CNI free)

Arm title	CNI low regimen
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Arm description:

CNI low regimen: comprising the following steps for switching treatment: Step 1 at BL2 + 1 day: Certican 1.5 mg, Sandimmun Optoral and corticosteroids Step 2 at BL2 + 8 days: Certican 1.5 mg, Sandimmun Optoral (low dose) and corticosteroids

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

Dosage and administration details:

Initially 1.5 mg/day, then based on blood level (3-8 ng/mL in CNI low regimen)

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: This study had two baselines. The first baseline was day of transplant. Subjects received a standard regimen and Simulect® and were followed for 3 months. At month 3, subjects' eligibility was re-evaluated for randomization. Baseline 2 (Month 3) was used for the analysis.

Number of subjects in period 2 ^[2]	Standard regimen	CNI free regimen	CNI low regimen
Started	166	171	162
Randomized-received treatment	165	171	161
Started - Extension	145	139	134
Completed - Extension	108 ^[3]	117	113 ^[4]
Started - Non-randomized - Extension	95 ^[5]	0 ^[6]	0 ^[7]
Completed - Non-randomized-Extension	1 ^[8]	0 ^[9]	0 ^[10]
Completed	127	110	124
Not completed	39	61	38
Adverse event, serious fatal	3	2	2
Consent withdrawn by subject	7	7	5
Adverse event, non-fatal	25	44	27
Administrative problems	1	1	2
Abnormal laboratory values	-	3	1
Protocol deviation	1	1	-
Lack of efficacy	2	3	1

Notes:

[2] - 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: The number of subjects who entered the follow-up phase was greater than the number that completed the previous phase. The milestones were created to capture the number of subjects who entered the follow-up phase which included subjects who discontinued early from the randomization phase and non-randomized subjects. Non-Randomized subjects had received the Standard regimen drug treatment.

[3] - 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 who entered the follow-up phase was greater than the number that completed the previous phase. The milestones were created to capture the number of subjects who entered the follow-up phase which included subjects who discontinued early from the randomization phase and non-randomized subjects. Non-Randomized subjects had received the Standard regimen drug treatment.

[4] - 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 who entered the follow-up phase was greater than the number that completed the previous phase. The milestones were created to capture the number of subjects who entered the follow-up phase which included subjects who discontinued early from the randomization phase and non-randomized subjects. Non-Randomized subjects had received the Standard regimen drug treatment.

[5] - 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 who entered the follow-up phase was greater than the number that completed the previous phase. The milestones were created to capture the number of subjects who entered the follow-up phase which included subjects who discontinued early from the randomization phase and non-randomized subjects. Non-Randomized subjects had received the Standard regimen drug treatment.

[6] - 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 who entered the follow-up phase was greater than the number that completed the previous phase. The milestones were created to capture the number of subjects who

entered the follow-up phase which included subjects who discontinued early from the randomization phase and non-randomized subjects. Non-Randomized subjects had received the Standard regimen drug treatment.

[7] - 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 who entered the follow-up phase was greater than the number that completed the previous phase. The milestones were created to capture the number of subjects who entered the follow-up phase which included subjects who discontinued early from the randomization phase and non-randomized subjects. Non-Randomized subjects had received the Standard regimen drug treatment.

[8] - 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 who entered the follow-up phase was greater than the number that completed the previous phase. The milestones were created to capture the number of subjects who entered the follow-up phase which included subjects who discontinued early from the randomization phase and non-randomized subjects. Non-Randomized subjects had received the Standard regimen drug treatment.

[9] - 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 who entered the follow-up phase was greater than the number that completed the previous phase. The milestones were created to capture the number of subjects who entered the follow-up phase which included subjects who discontinued early from the randomization phase and non-randomized subjects. Non-Randomized subjects had received the Standard regimen drug treatment.

[10] - 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 who entered the follow-up phase was greater than the number that completed the previous phase. The milestones were created to capture the number of subjects who entered the follow-up phase which included subjects who discontinued early from the randomization phase and non-randomized subjects. Non-Randomized subjects had received the Standard regimen drug treatment.

Baseline characteristics

Reporting groups

Reporting group title	Standard regimen
Reporting group description: Myfortic, Sandimmun Optoral and corticosteroids	
Reporting group title	CNI free regimen
Reporting group description: CNI free regimen: comprising the following steps for switching treatment: Step 1 at BL2 + 1 day: Myfortic, Certican 1.5 mg, Sandimmun Optoral (50% of standard dose) and corticosteroids Step 2 at BL2 + 8 days: Myfortic, Certican 3 mg and corticosteroids	
Reporting group title	CNI low regimen
Reporting group description: CNI low regimen: comprising the following steps for switching treatment: Step 1 at BL2 + 1 day: Certican 1.5 mg, Sandimmun Optoral and corticosteroids Step 2 at BL2 + 8 days: Certican 1.5 mg, Sandimmun Optoral (low dose) and corticosteroids	

Reporting group values	Standard regimen	CNI free regimen	CNI low regimen
Number of subjects	166	171	162
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)	147	158	150
From 65-84 years	19	13	12
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	49.9	48.9	48.6
standard deviation	± 11.8	± 12.5	± 12.3
Gender, Male/Female Units: Participants			
Female	65	69	61
Male	101	102	101

Reporting group values	Total		
Number of subjects	499		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	455		
From 65-84 years	44		
85 years and over	0		
Age Continuous Units: years arithmetic mean standard deviation	-		
Gender, Male/Female Units: Participants			
Female	195		
Male	304		

End points

End points reporting groups

Reporting group title	Standard regimen - Pre-phase
Reporting group description: Myfortic, Sandimmun Optoral, corticosteroids and Simulect® (if patient received transplant)	
Reporting group title	Standard regimen
Reporting group description: Myfortic, Sandimmun Optoral and corticosteroids	
Reporting group title	CNI free regimen
Reporting group description: CNI free regimen: comprising the following steps for switching treatment: Step 1 at BL2 + 1 day: Myfortic, Certican 1.5 mg, Sandimmun Optoral (50% of standard dose) and corticosteroids Step 2 at BL2 + 8 days: Myfortic, Certican 3 mg and corticosteroids	
Reporting group title	CNI low regimen
Reporting group description: CNI low regimen: comprising the following steps for switching treatment: Step 1 at BL2 + 1 day: Certican 1.5 mg, Sandimmun Optoral and corticosteroids Step 2 at BL2 + 8 days: Certican 1.5 mg, Sandimmun Optoral (low dose) and corticosteroids	
Subject analysis set title	Standard Regimen - Month 3 BL2 to Month 60
Subject analysis set type	Intention-to-treat
Subject analysis set description: Analysis set includes initial ITT population from Month 3 (BL2). LOCF method applied.	
Subject analysis set title	CNI free - Month 3 BL2 to Month 60
Subject analysis set type	Intention-to-treat
Subject analysis set description: Analysis set includes initial ITT population from Month 3 (BL2). LOCF method applied.	
Subject analysis set title	CNI low - Month 3 BL2 to Month 60
Subject analysis set type	Intention-to-treat
Subject analysis set description: Analysis set includes initial ITT population from Month 3 (BL2). LOCF method applied.	

Primary: Demonstrate superiority of a CNI free regimen in renal function assessed by GFR at Month 12 compared to the standard regimen

End point title	Demonstrate superiority of a CNI free regimen in renal function assessed by GFR at Month 12 compared to the standard regimen ^[1]
End point description: Change in GFR using the Nankivell formula ($GFR = 6.7 / Scr + BW / 4 - S_{urea} / 2 - 100 / (height)^2 + C$ where where Scr is the serum creatinine concentration expressed in mmol/L, BW the body weight in kilograms, S _{urea} the serum urea in mmol/L, height in m, and the constant C is 35 for male and 25 for female patients. The calculated GFR is expressed in mL/min per 1.73m ² , last observation carried forward (LOCF) was used for imputation of missing values, ANCOVA model, with treatment, center, donor type (deceased vs. living) as factors and BL2-value at V4/M3/BL2 as covariate. P-values are not adjusted	
End point type	Primary
End point timeframe: From randomization at BL2 (Month 3) to Month 12 post-transplant	
Notes:	

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The primary objective of this trial is to demonstrate superiority of a CNI free regimen with respect to renal function at Month 12 post-transplant assessed by GFR (Nankivell method) as compared to the standard regimen in de novo kidney transplant patients.

End point values	Standard regimen	CNI free regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	163		
Units: ml/min/1.73m ²				
least squares mean (confidence interval 95%)	63.03 (60.57 to 65.49)	68.59 (66.1 to 71.08)		

Statistical analyses

Statistical analysis title	BL2 (Month 3) to Month 12 in GFR-Nankivell Method
Comparison groups	Standard regimen v CNI free regimen
Number of subjects included in analysis	322
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	5.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.82
upper limit	8.31

Secondary: GFR in ml/min per 1.73m² (LOCF) change from Baseline 2, calculated via Nankivell formula at Month 12 (ITT population)

End point title	GFR in ml/min per 1.73m ² (LOCF) change from Baseline 2, calculated via Nankivell formula at Month 12 (ITT population)
End point description:	Change in GFR using the Nankivell formula ($GFR = 6.7 / Scr + BW / 4 - S_{urea} / 2 - 100 / (height)^2 + C$ where where Scr is the serum creatinine concentration expressed in mmol/L, BW the body weight in kilograms, S _{urea} the serum urea in mmol/L, height in m, and the constant C is 35 for male and 25 for female patients. The calculated GFR is expressed in mL/min per 1.73m ² , last observation carried forward (LOCF) was used for imputation of missing values, ANCOVA model, with treatment, center, donor type (deceased vs. living) as factors and BL2-value at V4/M3/BL2 as covariate.
End point type	Secondary
End point timeframe:	From randomization at BL2 (Month 3) to Month 12 post-transplant

End point values	Standard regimen	CNI free regimen	CNI low regimen	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	159	163	160	
Units: ml/min/1.73m ²				
least squares mean (confidence interval 95%)	63.03 (60.57 to 65.49)	68.59 (66.1 to 71.08)	63.08 (60.62 to 65.55)	

Statistical analyses

No statistical analyses for this end point

Secondary: GFR at Month 12 utilizing Modification of Diet in Renal Disease (MDRD) method

End point title	GFR at Month 12 utilizing Modification of Diet in Renal Disease (MDRD) method
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End point description:

Change in GFR (Modification of Diet in Renal Disease calculated using the –MDRD formulat: •For men: $GFR = 170 \times (\text{serum creatinine}^{-0.999}) \times (\text{age}^{-0.176}) \times (\text{urea nitrogen}^{-0.17}) \times (\text{albumin}^{0.318})$ • For women: $GFR = 170 \times (\text{serum creatinine}^{-0.999}) \times (\text{age}^{-0.176}) \times (\text{urea nitrogen}^{-0.17}) \times (\text{albumin}^{0.318}) \times 0.762$ with urea nitrogen = urea / 2.144.), last observation carried forward (LOCF) was used for imputation of missing values, ANCOVA model, with treatment, center, donor type (deceased vs. living) as factors and BL2-value at V4/M3/BL2 as covariate.

End point type	Secondary
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End point timeframe:

From randomization at BL2 (Month 3) to Month 12 post-transplant

End point values	Standard regimen	CNI free regimen	CNI low regimen	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	151	158	157	
Units: ml/min/1.73m ²				
least squares mean (confidence interval 95%)	50.23 (47.66 to 52.8)	56.36 (53.77 to 58.94)	50.24 (47.7 to 52.77)	

Statistical analyses

No statistical analyses for this end point

Secondary: GFR at Month 12 utilizing Cockcroft-Gault formula

End point title	GFR at Month 12 utilizing Cockcroft-Gault formula
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End point description:

Cockcroft-Gault formula: For men: $GFR = ((140 - \text{age}) \times \text{body weight in kg}) / (72 \times \text{serum creatinine in mg/dl})$ For women: $GFR = (0.85 \times (140 - \text{age}) \times \text{body weight in kg}) / (72 \times \text{serum creatinine in mg/dl})$, last observation carried forward (LOCF) was used for imputation of missing values, ANCOVA model

End point type	Secondary
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End point timeframe:

From randomization at BL2 (Month 3) to Month 12 post-transplant

End point values	Standard regimen	CNI free regimen	CNI low regimen	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	160	164	160	
Units: ml/min/1.73m ²				
least squares mean (confidence interval 95%)	60.18 (57.33 to 63.03)	64.87 (61.99 to 67.75)	61.16 (58.31 to 64.02)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change at Month 12 in serum creatine

End point title	Change at Month 12 in serum creatine
End point description: Change in venous blood serum creatinine,), last observation carried forward (LOCF) was used for imputation of missing values, ANCOVA model	
End point type	Secondary
End point timeframe: From randomization at BL2 (Month 3) to Month 12 post-transplant	

End point values	Standard regimen	CNI free regimen	CNI low regimen	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	160	165	160	
Units: mg/dl				
least squares mean (confidence interval 95%)	1.66 (1.51 to 1.81)	1.58 (1.43 to 1.73)	1.76 (1.61 to 1.91)	

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy event data from Baseline 2 (Month 3) to Month 6

End point title	Efficacy event data from Baseline 2 (Month 3) to Month 6
End point description: Efficacy events were: Biopsy-proven acute rejection (BPAR), graft loss, death, and treatment failure (defined as composite endpoint of BPAR, graft loss, death, loss to follow-up, discontinuation due to lack of efficacy or due to toxicity).	
End point type	Secondary
End point timeframe: From Baseline 2 (Month 3) to Month 6	

End point values	Standard regimen	CNI free regimen	CNI low regimen	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	165	171	161	
Units: Participants				
BPAR	6	15	10	
Graft loss	0	1	1	
Death	1	1	0	
Lost to follow-up	0	0	0	
Discontinuation due to lack of efficacy	1	2	1	
Discontinuation due to adverse event	8	26	13	
Therapy failure composite	14	37	19	

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy event data Baseline 2 (Month 3) to Month 12

End point title	Efficacy event data Baseline 2 (Month 3) to Month 12
End point description:	
Efficacy events were: Biopsy-proven acute rejection (BPAR), graft loss, death, and treatment failure (defined as composite endpoint of BPAR, graft loss, death, loss to follow-up, discontinuation due to lack of efficacy or due to toxicity).	
End point type	Secondary
End point timeframe:	
From Baseline 2 (Month 3) to Month 12	

End point values	Standard regimen	CNI free regimen	CNI low regimen	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	165	171	161	
Units: Participants				
BPAR	13	20	13	
Graft loss	1	2	1	
Death	3	2	2	
Lost to follow-up	0	0	0	
Discontinuation due to lack of efficacy	2	3	1	
Discontinuation due to adverse event	25	44	27	
Therapy failure composite	34	58	35	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from BL2 (Month 3) to Month 12 in Cardiovascular risk (Framingham score; 10-year Cardiovascular risk)

End point title	Change from BL2 (Month 3) to Month 12 in Cardiovascular risk (Framingham score; 10-year Cardiovascular risk)
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End point description:

The Framingham Score (based on LDL cholesterol level) estimates the coronary heart disease risk (%) of developing one of the following coronary heart diseases: angina pectoris, myocardial infarction, or coronary disease death, over the course of 10 years.

End point type	Secondary
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End point timeframe:

From Baseline 2 (Month 3) to Month 12

End point values	Standard regimen	CNI free regimen	CNI low regimen	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	165	171	161	
Units: Score of CHD Risk in 10 years				
arithmetic mean (standard deviation)				
Baseline 1/Visit 1	10.9 (± 8)	10.2 (± 7.4)	9.5 (± 6.9)	
Baseline 2/Month 3	10.3 (± 7.7)	8.8 (± 5.9)	9.3 (± 7.2)	
Month 12	9.4 (± 6.8)	9.1 (± 6.4)	8.7 (± 6.8)	
Change from Baseline 2 to Month 12	-0.7 (± 5.8)	0.4 (± 5.1)	-0.7 (± 5.4)	

Statistical analyses

No statistical analyses for this end point

Secondary: GFR calculated via Nankivell, Cockcroft, MDRD methods at Month 60 (ITT population)

End point title	GFR calculated via Nankivell, Cockcroft, MDRD methods at Month 60 (ITT population)
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End point description:

Change in GFR using the Nankivell formula ($GFR = 6.7 / Scr + BW / 4 - Surea / 2 - 100 / (height)^2 + C$ where where Scr is the serum creatinine concentration expressed in mmol/L, BW the body weight in kilograms, Surea the serum urea in mmol/L, height in m, and the constant C is 35 for male and 25 for female patients. The calculated GFR is expressed in mL/min per 1.73m², last observation carried forward (LOCF) was used for imputation of missing values, ANCOVA model, with treatment, center, donor type (deceased vs. living) as factors and BL2-value at V4/M3/BL2 as covariate.

End point type	Secondary
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End point timeframe:

From randomization at BL2 (Month 3) to Month 60

End point values	Standard Regimen - Month 3 BL2 to Month 60	CNI free - Month 3 BL2 to Month 60	CNI low - Month 3 BL2 to Month 60	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	162	165	159	
Units: ml/min/1.73m ²				
least squares mean (confidence interval 95%)				
Nankivell (160,163,159)	60.24 (57.11 to 63.38)	66.98 (63.78 to 70.17)	58.74 (55.58 to 61.9)	
Cockcroft (162,165,159)	55.92 (52.36 to 59.48)	61.6 (57.99 to 65.2)	52.91 (49.32 to 56.5)	
MDRD (152,159,156)	47.56 (44.58 to 50.54)	53.41 (50.4 to 56.42)	44.79 (41.83 to 47.74)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change at Month 60 in serum creatine

End point title	Change at Month 60 in serum creatine
End point description: Change in venous blood serum creatinine,), last observation carried forward (LOCF) was used for imputation of missing values, ANCOVA model	
End point type	Secondary
End point timeframe: From randomization at BL2 (Month 3) to Month 60 post-transplant	

End point values	Standard Regimen - Month 3 BL2 to Month 60	CNI free - Month 3 BL2 to Month 60	CNI low - Month 3 BL2 to Month 60	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	162	165	159	
Units: mg/dl				
least squares mean (confidence interval 95%)				
Serum creatinine (162,166,159)	1.94 (1.72 to 2.15)	1.69 (1.47 to 1.91)	2.01 (1.79 to 2.23)	

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy event data after Month 12 to Month 60

End point title	Efficacy event data after Month 12 to Month 60
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End point description:

Efficacy events were: Biopsy-proven acute rejection (BPAR), graft loss, death, and treatment failure (defined as composite endpoint of BPAR, graft loss, death, loss to follow-up, discontinuation due to lack of efficacy or due to toxicity).

End point type	Secondary
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End point timeframe:

Events starting after Month 12

End point values	Standard Regimen - Month 3 BL2 to Month 60	CNI free - Month 3 BL2 to Month 60	CNI low - Month 3 BL2 to Month 60	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	162	165	159	
Units: Participants				
BPAR (165,171,161)	13	13	12	
Graft loss(165,171,161)	7	7	3	
Death(165,171,161)	7	4	9	
Lost to follow-up(165,171,161)	17	15	13	
Discontinuation due to adverse event(165,171,161)	10	8	4	
Therapy failure (composite endpoint)(165,171,161)	38	35	36	

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 are reported in this record from 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
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Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Standard
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Reporting group description:

Standard

Reporting group title	CNI-free
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Reporting group description:

CNI-free

Reporting group title	CNI-low
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Reporting group description:

CNI-low

Serious adverse events	Standard	CNI-free	CNI-low
Total subjects affected by serious adverse events			
subjects affected / exposed	87 / 165 (52.73%)	91 / 171 (53.22%)	85 / 161 (52.80%)
number of deaths (all causes)	3	2	2
number of deaths resulting from adverse events	0	2	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B-CELL LYMPHOMA			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BASAL CELL CARCINOMA			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BRONCHIAL CARCINOMA			

subjects affected / exposed	1 / 165 (0.61%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	1 / 1	0 / 0
CLEAR CELL RENAL CELL CARCINOMA			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LIPOMA			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
METASTASES TO LIVER			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OVARIAN CANCER			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
POST TRANSPLANT LYMPHOPROLIFERATIVE DISORDER			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
RENAL CELL CARCINOMA			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SKIN PAPILLOMA			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SQUAMOUS CELL CARCINOMA			

subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
ARTERIAL HAEMORRHAGE			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ARTERIAL THROMBOSIS			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ARTERIOSCLEROSIS			
subjects affected / exposed	0 / 165 (0.00%)	2 / 171 (1.17%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ARTERIOVENOUS FISTULA			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEEP VEIN THROMBOSIS			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
EMBOLISM			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
EMBOLISM ARTERIAL			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERTENSION			

subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERTENSIVE CRISIS			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LYMPHOCELE			
subjects affected / exposed	2 / 165 (1.21%)	1 / 171 (0.58%)	4 / 161 (2.48%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LYMPHOEDEMA			
subjects affected / exposed	0 / 165 (0.00%)	0 / 171 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERIPHERAL ARTERY STENOSIS			
subjects affected / exposed	0 / 165 (0.00%)	0 / 171 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
THROMBOPHLEBITIS			
subjects affected / exposed	0 / 165 (0.00%)	0 / 171 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
THROMBOSIS			
subjects affected / exposed	0 / 165 (0.00%)	0 / 171 (0.00%)	3 / 161 (1.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VASCULITIS			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VENOUS ANEURYSM			

subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VENOUS OCCLUSION			
subjects affected / exposed	0 / 165 (0.00%)	0 / 171 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VENOUS THROMBOSIS			
subjects affected / exposed	0 / 165 (0.00%)	0 / 171 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VENOUS THROMBOSIS LIMB			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
RESUSCITATION			
subjects affected / exposed	0 / 165 (0.00%)	0 / 171 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
ATROPHY			
subjects affected / exposed	0 / 165 (0.00%)	0 / 171 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHILLS			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEVICE DISLOCATION			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GENERALISED OEDEMA			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
IMPAIRED HEALING			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LOCALISED OEDEMA			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MULTI-ORGAN FAILURE			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OEDEMA PERIPHERAL			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYREXIA			
subjects affected / exposed	1 / 165 (0.61%)	3 / 171 (1.75%)	4 / 161 (2.48%)
occurrences causally related to treatment / all	0 / 1	1 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUDDEN CARDIAC DEATH			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Immune system disorders			

DRUG HYPERSENSITIVITY			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
KIDNEY TRANSPLANT REJECTION			
subjects affected / exposed	5 / 165 (3.03%)	6 / 171 (3.51%)	4 / 161 (2.48%)
occurrences causally related to treatment / all	3 / 5	2 / 6	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TRANSPLANT REJECTION			
subjects affected / exposed	6 / 165 (3.64%)	13 / 171 (7.60%)	9 / 161 (5.59%)
occurrences causally related to treatment / all	2 / 6	5 / 13	6 / 13
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
OVARIAN CYST			
subjects affected / exposed	0 / 165 (0.00%)	2 / 171 (1.17%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VAGINAL HAEMORRHAGE			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
ALVEOLITIS ALLERGIC			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DYSPNOEA			
subjects affected / exposed	2 / 165 (1.21%)	3 / 171 (1.75%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PLEURAL FIBROSIS			

subjects affected / exposed	0 / 165 (0.00%)	0 / 171 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PLEURISY			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PRODUCTIVE COUGH			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PULMONARY EMBOLISM			
subjects affected / exposed	0 / 165 (0.00%)	2 / 171 (1.17%)	2 / 161 (1.24%)
occurrences causally related to treatment / all	0 / 0	0 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PULMONARY OEDEMA			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SLEEP APNOEA SYNDROME			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
ADJUSTMENT DISORDER			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEPRESSION			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PANIC ATTACK			

subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RESTLESSNESS			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
BLOOD CREATININE INCREASED			
subjects affected / exposed	14 / 165 (8.48%)	14 / 171 (8.19%)	17 / 161 (10.56%)
occurrences causally related to treatment / all	6 / 16	4 / 16	7 / 21
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CARBOHYDRATE ANTIGEN 125 INCREASED			
subjects affected / exposed	0 / 165 (0.00%)	0 / 171 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CREATININE URINE INCREASED			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CYTOMEGALOVIRUS TEST			
subjects affected / exposed	2 / 165 (1.21%)	0 / 171 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CYTOMEGALOVIRUS TEST POSITIVE			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMOGLOBIN DECREASED			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEPATIC ENZYME INCREASED			

subjects affected / exposed	0 / 165 (0.00%)	0 / 171 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
IMMUNOSUPPRESSANT DRUG LEVEL INCREASED			
subjects affected / exposed	0 / 165 (0.00%)	0 / 171 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RED BLOOD CELL ACANTHOCYTES PRESENT			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
WEIGHT INCREASED			
subjects affected / exposed	0 / 165 (0.00%)	0 / 171 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
ACCIDENT			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
ANKLE FRACTURE			
subjects affected / exposed	0 / 165 (0.00%)	0 / 171 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COMPLICATIONS OF TRANSPLANT SURGERY			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COMPLICATIONS OF TRANSPLANTED KIDNEY			

subjects affected / exposed	5 / 165 (3.03%)	0 / 171 (0.00%)	2 / 161 (1.24%)
occurrences causally related to treatment / all	2 / 5	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CONTUSION			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FEMORAL NECK FRACTURE			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FIBULA FRACTURE			
subjects affected / exposed	0 / 165 (0.00%)	0 / 171 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GRAFT LOSS			
subjects affected / exposed	0 / 165 (0.00%)	2 / 171 (1.17%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEAT STROKE			
subjects affected / exposed	0 / 165 (0.00%)	0 / 171 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INCISIONAL HERNIA			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
KIDNEY RUPTURE			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OVERDOSE			

subjects affected / exposed	0 / 165 (0.00%)	0 / 171 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
POST PROCEDURAL HAEMORRHAGE			
subjects affected / exposed	2 / 165 (1.21%)	0 / 171 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RENAL LYMPHOCELE			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SEROMA			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SHUNT OCCLUSION			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TIBIA FRACTURE			
subjects affected / exposed	0 / 165 (0.00%)	0 / 171 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TOXICITY TO VARIOUS AGENTS			
subjects affected / exposed	2 / 165 (1.21%)	0 / 171 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	2 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TRANSPLANT DYSFUNCTION			
subjects affected / exposed	0 / 165 (0.00%)	0 / 171 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TRANSPLANT FAILURE			

subjects affected / exposed	3 / 165 (1.82%)	5 / 171 (2.92%)	3 / 161 (1.86%)
occurrences causally related to treatment / all	1 / 3	4 / 5	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TRAUMATIC HAEMATOMA			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VENA CAVA INJURY			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
ACUTE CORONARY SYNDROME			
subjects affected / exposed	0 / 165 (0.00%)	2 / 171 (1.17%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ANGINA PECTORIS			
subjects affected / exposed	2 / 165 (1.21%)	0 / 171 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
AORTIC VALVE STENOSIS			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ATRIAL FIBRILLATION			
subjects affected / exposed	1 / 165 (0.61%)	2 / 171 (1.17%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ATRIAL FLUTTER			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BRADYCARDIA			

subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CARDIAC FAILURE			
subjects affected / exposed	1 / 165 (0.61%)	1 / 171 (0.58%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
CARDIAC FAILURE ACUTE			
subjects affected / exposed	0 / 165 (0.00%)	0 / 171 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
CORONARY ARTERY DISEASE			
subjects affected / exposed	0 / 165 (0.00%)	0 / 171 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
APHASIA			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CEREBRAL INFARCTION			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CEREBROVASCULAR ACCIDENT			
subjects affected / exposed	1 / 165 (0.61%)	2 / 171 (1.17%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEADACHE			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEMIPARESIS			

subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
POLYNEUROPATHY			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PRESYNCOPE			
subjects affected / exposed	0 / 165 (0.00%)	0 / 171 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
AGRANULOCYTOSIS			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ANAEMIA			
subjects affected / exposed	1 / 165 (0.61%)	1 / 171 (0.58%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BONE MARROW OEDEMA			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FEBRILE NEUTROPENIA			
subjects affected / exposed	0 / 165 (0.00%)	2 / 171 (1.17%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LEUKOPENIA			
subjects affected / exposed	0 / 165 (0.00%)	4 / 171 (2.34%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	5 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NEPHROGENIC ANAEMIA			

subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PANCYTOPENIA			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
POLYCYTHAEMIA			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
THROMBOCYTOPENIA			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
VERTIGO			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
CATARACT			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OPTIC ISCHAEMIC NEUROPATHY			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
ASCITES			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

COLITIS			
subjects affected / exposed	0 / 165 (0.00%)	2 / 171 (1.17%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIARRHOEA			
subjects affected / exposed	1 / 165 (0.61%)	5 / 171 (2.92%)	4 / 161 (2.48%)
occurrences causally related to treatment / all	1 / 1	1 / 5	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTRITIS			
subjects affected / exposed	0 / 165 (0.00%)	0 / 171 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMATOCHESIA			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMORRHOIDAL HAEMORRHAGE			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMORRHOIDS			
subjects affected / exposed	0 / 165 (0.00%)	0 / 171 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NAUSEA			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NONINFECTIOUS PERITONITIS			

subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RECTAL PERFORATION			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
UPPER GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VOMITING			
subjects affected / exposed	1 / 165 (0.61%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
CHOLECYSTITIS ACUTE			
subjects affected / exposed	0 / 165 (0.00%)	0 / 171 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHOLELITHIASIS			
subjects affected / exposed	0 / 165 (0.00%)	0 / 171 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
SKIN ULCER			
subjects affected / exposed	0 / 165 (0.00%)	0 / 171 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
ACUTE KIDNEY INJURY			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	2 / 161 (1.24%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

GLOMERULOSCLEROSIS subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 165 (0.61%) 0 / 1 0 / 0	0 / 171 (0.00%) 0 / 0 0 / 0	0 / 161 (0.00%) 0 / 0 0 / 0
HAEMATURIA subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	2 / 165 (1.21%) 0 / 2 0 / 0	0 / 171 (0.00%) 0 / 0 0 / 0	1 / 161 (0.62%) 0 / 1 0 / 0
HYDRONEPHROSIS subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 165 (0.00%) 0 / 0 0 / 0	0 / 171 (0.00%) 0 / 0 0 / 0	1 / 161 (0.62%) 0 / 1 0 / 0
KIDNEY FIBROSIS subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 165 (0.00%) 0 / 0 0 / 0	1 / 171 (0.58%) 0 / 1 0 / 0	0 / 161 (0.00%) 0 / 0 0 / 0
NEPHRECTASIA subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 165 (0.61%) 0 / 1 0 / 0	0 / 171 (0.00%) 0 / 0 0 / 0	0 / 161 (0.00%) 0 / 0 0 / 0
NEPHROLITHIASIS subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 165 (0.00%) 0 / 0 0 / 0	0 / 171 (0.00%) 0 / 0 0 / 0	1 / 161 (0.62%) 0 / 1 0 / 0
NEPHROPATHY subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 165 (0.00%) 0 / 0 0 / 0	0 / 171 (0.00%) 0 / 0 0 / 0	1 / 161 (0.62%) 0 / 1 0 / 0
PROTEINURIA subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 165 (0.00%) 0 / 0 0 / 0	3 / 171 (1.75%) 2 / 3 0 / 0	1 / 161 (0.62%) 0 / 1 0 / 0
REFLUX NEPHROPATHY			

subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RENAL ARTERY STENOSIS			
subjects affected / exposed	2 / 165 (1.21%)	2 / 171 (1.17%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RENAL CYST RUPTURED			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RENAL FAILURE			
subjects affected / exposed	0 / 165 (0.00%)	0 / 171 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RENAL IMPAIRMENT			
subjects affected / exposed	2 / 165 (1.21%)	0 / 171 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RENAL INFARCT			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RENAL TUBULAR ATROPHY			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TUBULOINTERSTITIAL NEPHRITIS			
subjects affected / exposed	0 / 165 (0.00%)	0 / 171 (0.00%)	2 / 161 (1.24%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URETERIC STENOSIS			

subjects affected / exposed	2 / 165 (1.21%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URETHRAL OBSTRUCTION			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URETHRAL STENOSIS			
subjects affected / exposed	2 / 165 (1.21%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY RETENTION			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY TRACT OBSTRUCTION			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VESICoureTERIC REFLUX			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
ARTHROPATHY			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
JOINT SWELLING			
subjects affected / exposed	0 / 165 (0.00%)	0 / 171 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MUSCULAR WEAKNESS			

subjects affected / exposed	0 / 165 (0.00%)	0 / 171 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MYALGIA			
subjects affected / exposed	0 / 165 (0.00%)	0 / 171 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MYOSITIS			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NEUROPATHIC ARTHROPATHY			
subjects affected / exposed	0 / 165 (0.00%)	0 / 171 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OSTEONECROSIS			
subjects affected / exposed	2 / 165 (1.21%)	0 / 171 (0.00%)	2 / 161 (1.24%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
POST TRANSPLANT DISTAL LIMB SYNDROME			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RHABDOMYOLYSIS			
subjects affected / exposed	0 / 165 (0.00%)	0 / 171 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
ANORECTAL INFECTION			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
APPENDICITIS			

subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ATYPICAL PNEUMONIA			
subjects affected / exposed	2 / 165 (1.21%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BK VIRUS INFECTION			
subjects affected / exposed	0 / 165 (0.00%)	0 / 171 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BRONCHITIS			
subjects affected / exposed	2 / 165 (1.21%)	0 / 171 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BRONCHOPNEUMONIA			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	2 / 161 (1.24%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CANDIDA INFECTION			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CYSTITIS			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CYTOMEGALOVIRUS GASTROENTERITIS			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CYTOMEGALOVIRUS INFECTION			

subjects affected / exposed	6 / 165 (3.64%)	1 / 171 (0.58%)	4 / 161 (2.48%)
occurrences causally related to treatment / all	1 / 6	0 / 1	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CYTOMEGALOVIRUS VIRAEMIA			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIABETIC GANGRENE			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIARRHOEA INFECTIOUS			
subjects affected / exposed	0 / 165 (0.00%)	0 / 171 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ENCEPHALITIS			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
EPSTEIN-BARR VIRUS INFECTION			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ESCHERICHIA INFECTION			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FEBRILE INFECTION			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	2 / 161 (1.24%)
occurrences causally related to treatment / all	0 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GANGRENE			

subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROENTERITIS			
subjects affected / exposed	3 / 165 (1.82%)	6 / 171 (3.51%)	2 / 161 (1.24%)
occurrences causally related to treatment / all	0 / 3	1 / 6	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROENTERITIS NOROVIRUS			
subjects affected / exposed	1 / 165 (0.61%)	1 / 171 (0.58%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROINTESTINAL INFECTION			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	2 / 161 (1.24%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GROIN ABSCESS			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMATOMA INFECTION			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HERPES ZOSTER			
subjects affected / exposed	2 / 165 (1.21%)	1 / 171 (0.58%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 2	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INFECTION			
subjects affected / exposed	4 / 165 (2.42%)	1 / 171 (0.58%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	3 / 4	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INFLUENZA			

subjects affected / exposed	0 / 165 (0.00%)	0 / 171 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
KIDNEY INFECTION			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LOWER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NECROTISING FASCIITIS			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
PNEUMOCYSTIS JIROVECI PNEUMONIA			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA			
subjects affected / exposed	3 / 165 (1.82%)	6 / 171 (3.51%)	4 / 161 (2.48%)
occurrences causally related to treatment / all	1 / 4	4 / 7	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA CYTOMEGALOVIRAL			
subjects affected / exposed	0 / 165 (0.00%)	2 / 171 (1.17%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA INFLUENZAL			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA STREPTOCOCCAL			

subjects affected / exposed	0 / 165 (0.00%)	0 / 171 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PSEUDOMEMBRANOUS COLITIS			
subjects affected / exposed	0 / 165 (0.00%)	0 / 171 (0.00%)	2 / 161 (1.24%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYELONEPHRITIS			
subjects affected / exposed	1 / 165 (0.61%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYONEPHROSIS			
subjects affected / exposed	0 / 165 (0.00%)	0 / 171 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RENAL CYST INFECTION			
subjects affected / exposed	1 / 165 (0.61%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SALPINGO-OOPHORITIS			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SEPSIS			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
SEPTIC SHOCK			

subjects affected / exposed	0 / 165 (0.00%)	0 / 171 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SHUNT INFECTION			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SINUSITIS			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
STAPHYLOCOCCAL INFECTION			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY TRACT INFECTION			
subjects affected / exposed	15 / 165 (9.09%)	12 / 171 (7.02%)	7 / 161 (4.35%)
occurrences causally related to treatment / all	11 / 19	4 / 13	5 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
UROSEPSIS			
subjects affected / exposed	6 / 165 (3.64%)	2 / 171 (1.17%)	7 / 161 (4.35%)
occurrences causally related to treatment / all	3 / 7	0 / 2	4 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VARICELLA			
subjects affected / exposed	1 / 165 (0.61%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VIRAL INFECTION			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
WOUND INFECTION			

subjects affected / exposed	1 / 165 (0.61%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
DEHYDRATION			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	2 / 161 (1.24%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIABETES MELLITUS			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOCALCAEMIA			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOGLYCAEMIA			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TUMOUR LYSIS SYNDROME			
subjects affected / exposed	1 / 165 (0.61%)	0 / 171 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
TYPE 2 DIABETES MELLITUS			
subjects affected / exposed	0 / 165 (0.00%)	1 / 171 (0.58%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Standard	CNI-free	CNI-low
Total subjects affected by non-serious adverse events subjects affected / exposed	121 / 165 (73.33%)	134 / 171 (78.36%)	133 / 161 (82.61%)
Investigations BLOOD CREATININE INCREASED subjects affected / exposed occurrences (all)	14 / 165 (8.48%) 17	11 / 171 (6.43%) 12	12 / 161 (7.45%) 13
Vascular disorders HYPERTENSION subjects affected / exposed occurrences (all)	10 / 165 (6.06%) 10	5 / 171 (2.92%) 5	10 / 161 (6.21%) 10
Nervous system disorders HEADACHE subjects affected / exposed occurrences (all)	7 / 165 (4.24%) 7	11 / 171 (6.43%) 12	10 / 161 (6.21%) 13
Blood and lymphatic system disorders ANAEMIA subjects affected / exposed occurrences (all) LEUKOPENIA subjects affected / exposed occurrences (all)	5 / 165 (3.03%) 5 22 / 165 (13.33%) 24	14 / 171 (8.19%) 14 26 / 171 (15.20%) 31	2 / 161 (1.24%) 2 18 / 161 (11.18%) 19
General disorders and administration site conditions OEDEMA subjects affected / exposed occurrences (all) OEDEMA PERIPHERAL subjects affected / exposed occurrences (all)	15 / 165 (9.09%) 15 9 / 165 (5.45%) 9	14 / 171 (8.19%) 14 17 / 171 (9.94%) 17	22 / 161 (13.66%) 22 28 / 161 (17.39%) 32
Gastrointestinal disorders APHTHOUS STOMATITIS subjects affected / exposed occurrences (all) DIARRHOEA subjects affected / exposed occurrences (all) NAUSEA	1 / 165 (0.61%) 1 17 / 165 (10.30%) 19	33 / 171 (19.30%) 38 34 / 171 (19.88%) 37	14 / 161 (8.70%) 18 15 / 161 (9.32%) 15

subjects affected / exposed occurrences (all)	5 / 165 (3.03%) 5	8 / 171 (4.68%) 9	9 / 161 (5.59%) 9
Respiratory, thoracic and mediastinal disorders COUGH subjects affected / exposed occurrences (all)	11 / 165 (6.67%) 13	8 / 171 (4.68%) 9	7 / 161 (4.35%) 7
Renal and urinary disorders PROTEINURIA subjects affected / exposed occurrences (all)	3 / 165 (1.82%) 3	6 / 171 (3.51%) 7	13 / 161 (8.07%) 14
Musculoskeletal and connective tissue disorders ARTHRALGIA subjects affected / exposed occurrences (all)	2 / 165 (1.21%) 2	11 / 171 (6.43%) 12	7 / 161 (4.35%) 8
Infections and infestations CYTOMEGALOVIRUS INFECTION subjects affected / exposed occurrences (all)	12 / 165 (7.27%) 14	8 / 171 (4.68%) 8	4 / 161 (2.48%) 4
NASOPHARYNGITIS subjects affected / exposed occurrences (all)	29 / 165 (17.58%) 31	36 / 171 (21.05%) 45	37 / 161 (22.98%) 44
URINARY TRACT INFECTION subjects affected / exposed occurrences (all)	37 / 165 (22.42%) 43	31 / 171 (18.13%) 45	32 / 161 (19.88%) 47
Metabolism and nutrition disorders HYPERCHOLESTEROLAEMIA subjects affected / exposed occurrences (all)	4 / 165 (2.42%) 4	8 / 171 (4.68%) 8	18 / 161 (11.18%) 18
HYPERLIPIDAEMIA subjects affected / exposed occurrences (all)	4 / 165 (2.42%) 4	6 / 171 (3.51%) 6	11 / 161 (6.83%) 11
HYPERURICAEMIA subjects affected / exposed occurrences (all)	9 / 165 (5.45%) 9	3 / 171 (1.75%) 3	4 / 161 (2.48%) 4
HYPOKALAEMIA			

subjects affected / exposed	10 / 165 (6.06%)	20 / 171 (11.70%)	6 / 161 (3.73%)
occurrences (all)	10	22	6
IRON DEFICIENCY			
subjects affected / exposed	10 / 165 (6.06%)	7 / 171 (4.09%)	7 / 161 (4.35%)
occurrences (all)	10	7	7

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 January 2008	Amendment was issued approximately 6 months after FPFV changed the lower target therapeutic limit for Certican whole blood trough levels in the CNI free regimen from 6 ng/ml to 5 ng/ml, addressed the assessment and follow-up of patients after Month 12/ End of Study (recording of information) and the SAE reporting of patients in the extension period.
26 January 2009	Amendment added a post-text supplement to describe optional biomarker assessments to be performed as a sub-study.
01 February 2010	Amendment addressed the documentation of AEs, concomitant medication and immunosuppressive medication for patients who were or were not randomized. Additionally, several inconsistencies within the protocol were corrected.
16 May 2011	Amendment addressed the SAE reporting of patients suffering from rejection.
27 October 2011	Amendment was issued when recruitment was 100% complete and addressed the follow-up of patients who were not randomized and who were to be followed up in the former version of the protocol for additional four years. These patients never received the foreseen treatment in the protocol and therefore no additional information would be generated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Milestones were added to Subject Disposition for subjects entering and completing the extension period which included randomized subjects from treatment period and non-randomized subjects from Pre-phase Period.

Notes: